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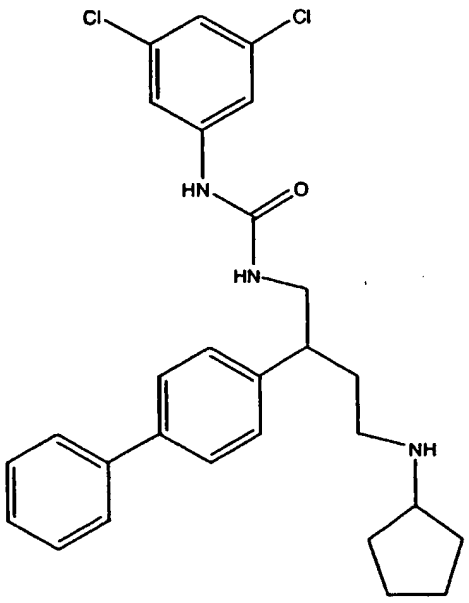
(54) Title: ARYL AND BIARYL COMPOUNDS HAVING MCH MODULATORY ACTIVITY



(I)

(57) Abstract: In one embodiment, this invention provides a novel class of compounds as antagonists of the MCH receptor, methods of preparing such compounds, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention or amelioration or one or more of diseases associated with the MCH receptor. An illustrative inventive compound is shown here.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ARYL AND BIARYL COMPOUNDS HAVING MCH MODULATORY ACTIVITY

Field of the Invention

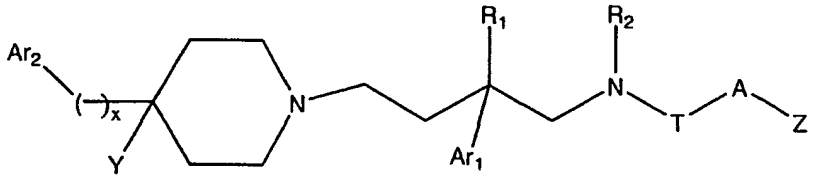
The present invention relates to antagonists for melanin-concentrating hormone (MCH) and their use in the treatment of obesity, diabetes and related disorders. It generally discloses novel compounds having MCH receptor modulatory activity, pharmaceutical compositions containing one or more such modulators, methods of preparing such modulators and methods of using such modulators to treat obesity, diabetes and related disorders. The invention specifically discloses certain novel aryl and biaryl compounds. This application claims priority from U.S. provisional patent application, Serial Number 60/277,534 filed March 21, 2001.

Background of the Invention

MCH, a 19-amino acid cyclic peptide, was first identified over a decade ago in teleost fish where it appears to regulate color change. More recently, MCH which is synthesized mainly in the lateral hypothalamus, a brain center regulating feeding behavior, has been the subject of investigation for its possible role as a regulator of eating behavior in mammals. Central administration of MCH is known to stimulate food intake and promote fat storage in rodents. It is also known that mice that over-express MCH are obese. As reported by Shimada *et al.*, *Nature*, Vol. 396 (17 Dec. 1998), pp. 670-673, MCH-deficient mice have reduced body weight and leanness due to hypophagia (reduced feeding). In view of their findings, the authors have suggested that antagonists of MCH action may be effective for the treatment of obesity. U.S. Patent No. 5,908,830 discloses a combination therapy for the treatment of diabetes or obesity involving the administration of a metabolic rate increasing agent and a feeding behavior modifying agent, an example of the latter being an MCH antagonist. U.S. Patent No. 6,043,246 discloses urea derivatives said to be useful as neuropeptide Y receptor antagonists and as agents for the treatment of, *inter alia*, diseases of the metabolic system including obesity

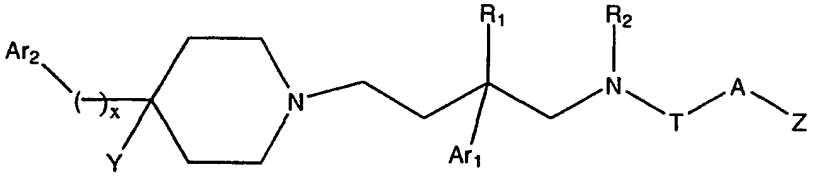
and diabetes. Published PCT patent application WO 00/27845 describes a class of compounds, characterized therein as spiro-indolines, said to be selective neuropeptide Y Y5 antagonists and useful for the treatment of obesity and the complications associated therewith. Commonly assigned, copending U.S. provisional patent application Serial No. 60/232,255, filed September 14, 2000, discloses and claims aryl-substituted urea neuropeptide Y Y5 antagonists and their use in the treatment of obesity, hyperphagia (increased feeding) and diabetes.

GB 2304714-A (Assignee: Sanofi) discloses piperidine derivatives of the formula:



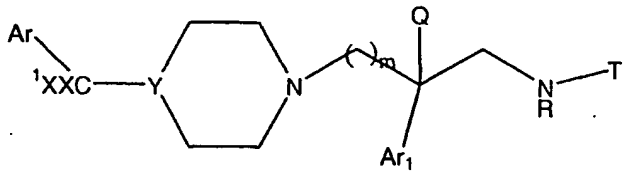
where the various moieties are as defined.

FR 2717802-A1 discloses piperidines of the formula:



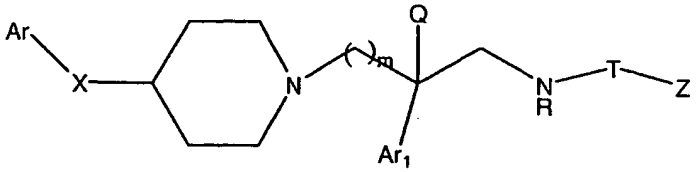
where the various moieties are as defined.

EP 428434-A discloses piperidines and piperazines of the formula:



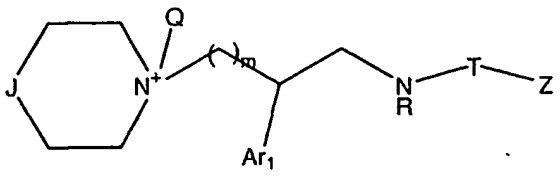
where the various moieties are as defined.

EP 515240-A1 discloses compounds of the formula:



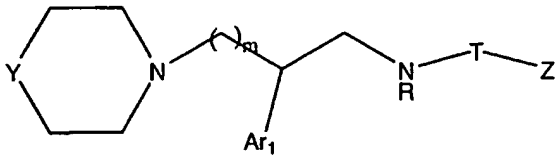
where the various moieties are as defined.

EP 559538-A1 discloses compounds of the formula:



where the various moieties are as defined.

EP 474561-A1 discloses compounds of the formula:



where the various moieties are as defined.

Copending patent application, Serial No. _____ , filed of even date herewith, discloses certain novel compounds with MCH modulatory activity.

There is a need for new compounds, formulations, treatments and therapies for MCH receptor modulation, diabetes and related disorders . It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such disorders.

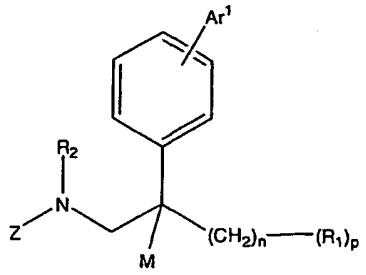
A further object of the present invention is to provide methods for modulating the MCH receptor using the compounds and pharmaceutical compositions provided herein.

Another object herein is to provide methods of modulating MCH receptors using the compounds provided herein.

Summary of the Invention

In its many embodiments, the present invention provides a novel class of compounds as antagonists of MCH receptor, methods of preparing such compounds, pharmaceutical compositions containing one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention or amelioration of

one or more diseases associated with the MCH receptor. In one embodiment, the present application discloses a compound, including enantiomers, stereoisomers, rotamers, tautomers and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound or of said prodrug, said compound having the general structure shown in Formula I:



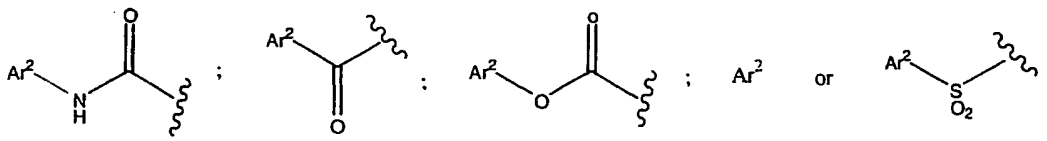
Formula I

wherein:

Ar^1 = unsubstituted or substituted phenyl, pyridine, pyridine-N-oxide, pyrazine or pyridazine, wherein the substituents number from 0 to 5, may be the same or different and are independently selected from the group consisting of H, CN, OCF_3, F, Cl, Br, I, $CONH_2$, methylenedioxy, OR, CO_2H, CO_2R, and OH with R being a C_1-C_6 straight chain alkyl or branched alkyl or a C_3-C_7 cycloalkyl;

M is H or R;

Z =

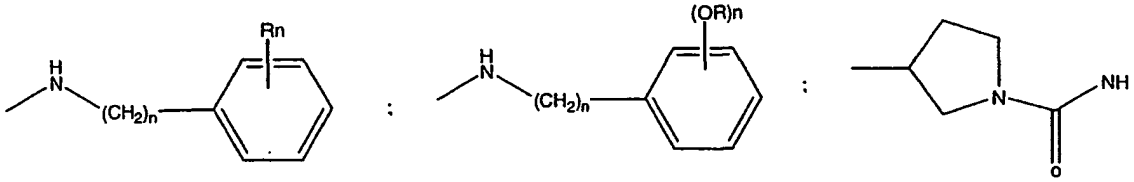


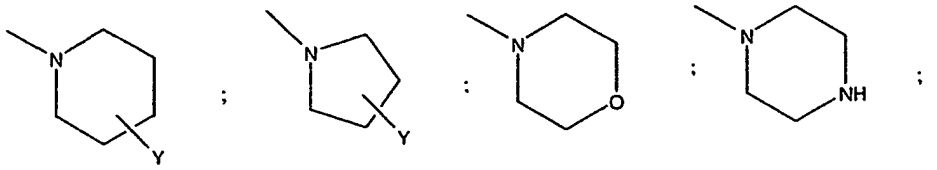
where Ar^2 is an unsubstituted or substituted phenyl wherein the substituents number from 0 to 5, may be the same or different and are independently selected from the group consisting F, Cl, Br, I, R, OR, NO_2, and CF_3;

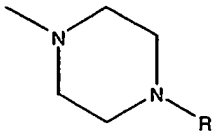
n = 0 to 6;

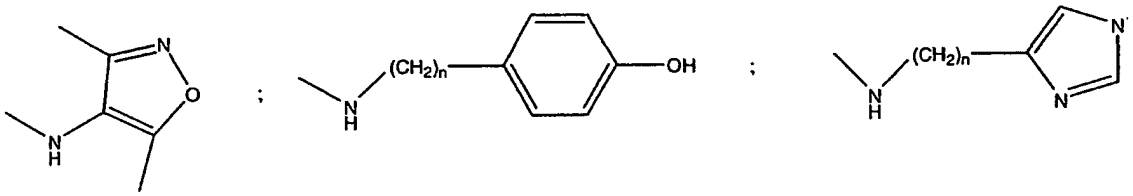
p = 1-6;

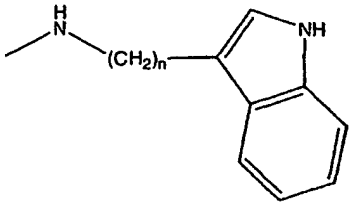
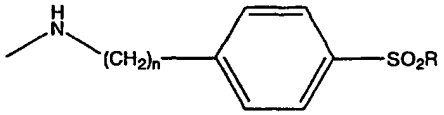
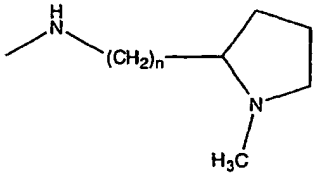
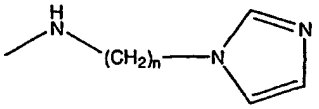
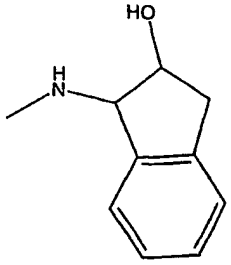
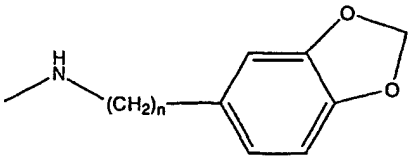
R_1 may be the same or different and is independently selected from the group consisting of R; NH_2; NHR; $N(R)_2$; $N(R)_2 \rightarrow O$; $NH(CH_2)_nOR$; $N(R)SO_2R$; $NH(CH_2)_n$-$N(R)_2$; $N(R)SO_2(R)$;







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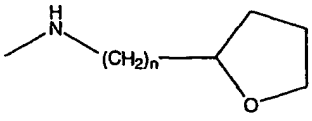
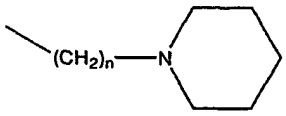
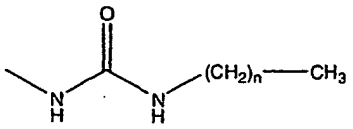
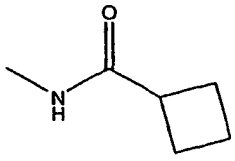
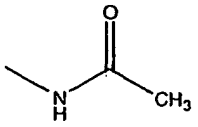
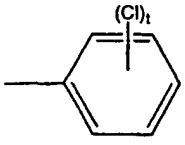
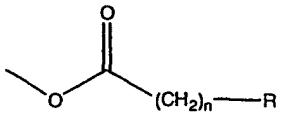
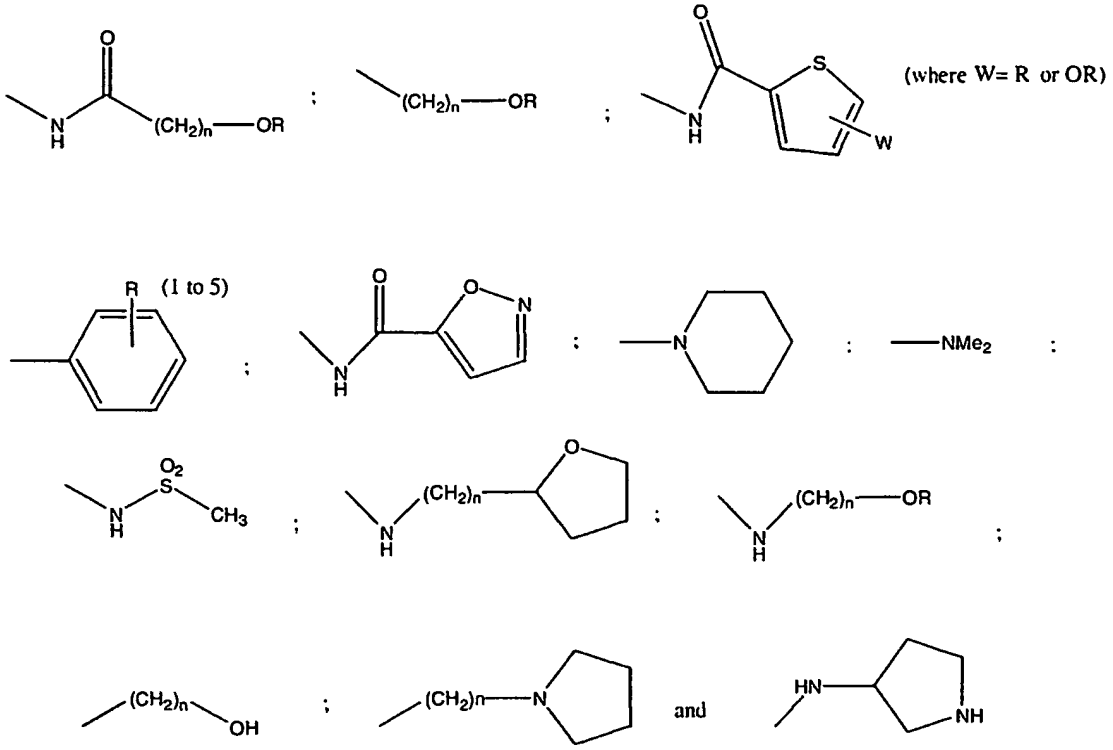


where n is defined above and where Y is a moiety numbering 0 to 5 which may be the same or different and are independently selected from the group consisting of H; OH; NH_2;



where n is defined above and t = 1 to 5;

and R_2 is H or alkyl.

The preferred representations for the various functionalities in Formula I are:

For Ar^1: phenyl or pyridyl (more preferably 4-phenyl or 4-pyridyl on the ring in Formula I), with one or more substituents on said phenyl or pyridyl independently selected from the group consisting of CN, OCF_3 and halogen, more preferably a phenyl with substituents selected from CN, OCF_3, F and Cl, and still more preferably when at least one of these preferred substituents is in position 3 or position 4 on the ring with respect to said ring's attachment to the benzylic position shown in Formula I.

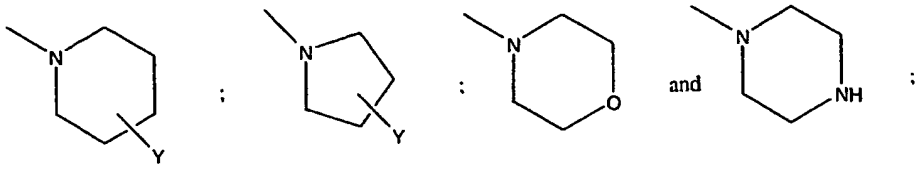
For Z: Ar^2-NH-CO, where Ar^2 is a phenyl which may optionally be substituted with 1-5 moieties such as a halogen, OCH_3 or CF_3, more preferably the substituent being F, Cl or OCH_3.

For R: preferably a C_1-C_4 straight chain or branched alkyl or a C_3-C_7 cycloalkyl.

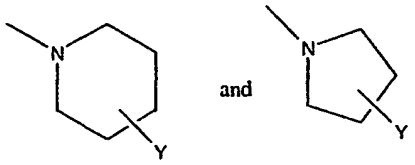
For n: preferably 1-6, more preferably 2-4, and still more preferably 2.

For M: H.

For R_1: preferably selected from the group consisting of NHR; $N(R)_2$; $N(R)_2 \longrightarrow O$; $NH(CH_2)_nOCH_3$; $N(R)SO_2R$; $NH(CH_2)_n$-$N(R)_2$; $N(R)SO_2(R)$;

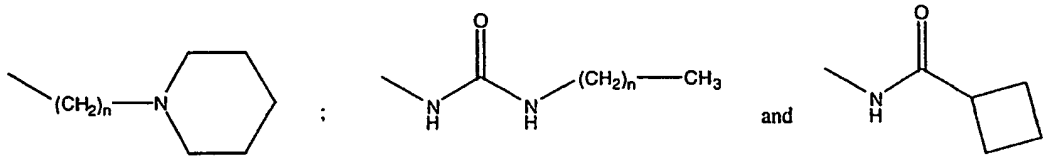


with the more preferable moieties being NHMe; NHEt; NMe_2; $NH(CH_2)_nOCH_3$; NH-cyclopropyl; NH-cyclobutyl; NH-cyclopentyl; $NH(CH_2)_3NMe_2$; and

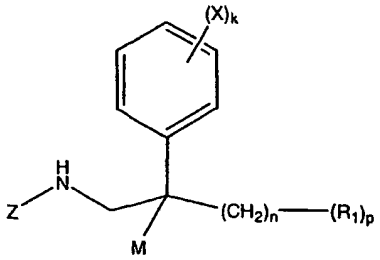


where Y and n are as defined above.

For Y: preferably the moieties NH_2; NMe_2; NHMe;



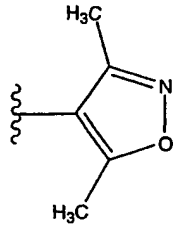
The present invention also discloses a compound, including enantiomers, stereoisomers, rotamers, tautomers and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound or of said prodrug, said compound having the general structure shown in Formula II:



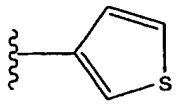
Formula II

where M, Z, n, p and R_1 are defined above along with their preferences; k is a number from 0 to 5. X may be the same or different, and is independently selected from the group consisting of:

H, Cl, F, Br, I, R, OR, CF_3, OCF_3, methylenedioxy,

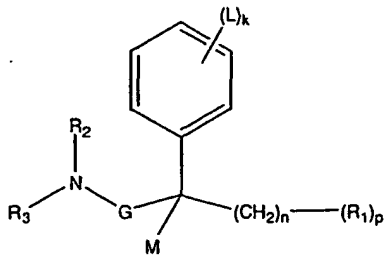


and



with the preferred moieties for X being R, H, Cl, CF_3 and OCF_3. The number k is preferably 1-3.

The present invention additionally discloses a compound, including enantiomers, stereoisomers, rotamers, tautomers and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound or of said prodrug, said compound having the general structure shown in Formula III:



Formula III

where M, n, p and R_1 are defined above along with their preferences. R_2 is H or alkyl and k is a number 0 to 5. G is $-CH_2-$, -C(O)- or –C(O)-O- with the –C(O) linked to the $N(R_1R_2)$ in the figure. R_3 is an alkyl, aryl, arylalkyl or alkylaryl. L may be the same or different and is independently selected from the group consisting of H, aryl, alkyl, halogen, alkoxy, aryloxy, arylalkoxy, alkylaryloxy, hydroxy, carboxy, carboalkoxy, cyano, CF_3 and NO_2.

The ring moieties in the inventive compounds may optionally carry substituents or additional substituents on the ring. Such substituents may be, for

example, R, halogen, alkoxy, aryloxy, arylalkoxy, alkylaryloxy, hydroxy, carboxy, carboalkoxy, cyano, trifluoroalkyl, nitro and the like.

Also included in the invention are tautomers, rotamers, enantiomers and other optical isomers of compounds of Formula I, Formula II and Formula III where applicable, pharmaceutically acceptable salts, solvates and derivatives thereof, as well as prodrug of said compounds, and pharmaceutically acceptable salts, solvates and derivatives of said prodrug.

A further feature of the invention is pharmaceutical compositions containing as active ingredient a compound of Formula I, Formula II or Formula III (or its salt, solvate or isomers) together with a pharmaceutically acceptable carrier or excipient.

The invention also provides methods for preparing compounds of Formula I, Formula II and Formula III, as well as methods for treating diseases such as, for example, obesity and related disorders. The methods for treating comprise administering to a patient suffering from said disease or diseases therapeutically effective amounts of a compound of Formula I, Formula II or Formula III, or of pharmaceutical compositions comprising a compound of Formula I, Formula II or Formula III. The term "Therapeutically effective amounts" refers to amounts of the compound that are effective to make the compound function as MCH modulator.

Also disclosed is the use of a compound of Formula I, Formula II or of Formula III for the manufacture of a medicament for treating obesity and related disorders.

In addition to monotherapies including the compound represented by Formula I, Formula II or Formula III, another aspect of this invention is combinations (such as, for example, dual combination therapy, three combination therapy and the like,) of therapeutically effective amounts of a compound of Formula I (or Formula II or Formula III), or a prodrug thereof, or a pharmaceutically acceptable salt of said compound or a pharmaceutically acceptable salt of said prodrug, and therapeutically effective amounts of one or more antiobesity / anorectic agent such as, for example, a β_3 agonist, a thyromimetic agent, or an NPY antagonist .

Still another aspect of this invention is a method for treating obesity comprising administering to a mammal (which term includes humans) in need of such treatment:

a. therapeutically effective amounts of a first compound, said first compound being a Formula I compound (or a Formula II compound or a Formula III compound), a prodrug thereof, or a pharmaceutically acceptable salt of said compound or a pharmaceutically acceptable salt of said prodrug; and

b. therapeutically effective amounts of a second compound, said second compound being an antiobesity and/or anorectic agent such as, for example, a β_3 agonist, a thyromimetic agent, or an NPY antagonist, wherein the amounts of the first and second compounds result in the desired therapeutic effect of treating obesity.

This invention is also directed to a pharmaceutical composition comprising a combination of therapeutically effective amounts of a first compound, said first compound being a Formula I compound (or a Formula II compound or a Formula III compound), a prodrug thereof, or a pharmaceutically acceptable salt of said compound or a pharmaceutically acceptable salt of said prodrug; and therapeutically effective amounts of a second compound, said second compound being an antiobesity and/or anorectic agent such as, for example, a β_3 agonist, a thyromimetic agent, or an NPY antagonist; and/or optionally a pharmaceutical acceptable carrier, vehicle or diluent.

Another aspect of this invention is a kit comprising:

a. therapeutically effective amounts of a first compound, said first compound being a Formula I compound (or a Formula II compound or a Formula III compound), a prodrug thereof, or a pharmaceutically acceptable salt of said compound or a pharmaceutically acceptable salt of said prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;

b. therapeutically effective amounts of a second compound, said second compound being an antiobesity and/or anorectic agent such as, for example, a β_3 agonist, a thyromimetic agent, or an NPY antagonist; and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and

c. means for containing said first unit dosage form and said second unit dosage form, wherein the amounts of the first compound and of the second compound result in the desired therapeutic effect of treating obesity.

Illustrative non-limiting examples of preferred antiobesity and/or anorectic agents in the above combination methods, combination compositions and combination kits include: phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A (hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as, for example, sibutramine), a sympathomimetic agent, a serotonergic agent (such as, for example, dexfenfluramine or fenfluramine), a dopamine agonist (such as, for example, bromocriptine), a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, the OB protein (hereinafter referred to as "leptin"), a leptin analog, a leptin receptor agonist, a galanin antagonist or a GI lipase inhibitor or decreaser (such as orlistat). Other anorectic agents include bombesin agonists, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the glucagon-like peptide-1 receptor such as, for example, Exendin and ciliary neurotrophic factors such as, for example, Axokine.

Another aspect of this invention is a method for treating diabetes comprising administering to a mammal:

a. therapeutically effective amounts of a first compound, said first compound being a Formula I compound (or a Formula II compound or a Formula III compound), a prodrug thereof, or a pharmaceutically acceptable salt of said compound or a pharmaceutically acceptable salt of said prodrug; and

b. therapeutically effective amounts of a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase 1B inhibitor, a dipeptidyl protease inhibitor, insulin (including orally bioavailable insulin preparations), an insulin mimetic, metformin, acarbose, a PPAR-gamma ligand such as troglitazone, rosaglitazone, pioglitazone or GW-1929, a sulfonylurea,

glipazide, glyburide, or chlorpropamide wherein the amounts of the first and second compounds result in the therapeutic effect of treating diabetes.

This invention is also directed to a pharmaceutical composition comprising a combination of therapeutically effective amounts of a first compound, said first compound being a Formula I compound (or a Formula II compound or a Formula III compound), a prodrug thereof, or a pharmaceutically acceptable salt of said compound or a pharmaceutically acceptable salt of said prodrug; therapeutically effective amounts of a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase 1B inhibitor, a dipeptidyl protease inhibitor, insulin (including orally bioavailable insulin preparations), an insulin mimetic, metformin, acarbose, a PPAR-gamma ligand such as troglitazone, rosaglitazone, pioglitazone, or GW-1929, a sulfonylurea, glipazide, glyburide, or chlorpropamide; and optionally

a pharmaceutically acceptable carrier, vehicle or diluent.

Another aspect of this invention is a kit comprising:

a. therapeutically effective amounts of a first compound, said first compound being a Formula I compound (or a Formula II compound or a Formula III compound), a prodrug thereof, or a pharmaceutically acceptable salt of said compound or a pharmaceutically acceptable salt of said prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;

b. therapeutically effective amounts of an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase 1B inhibitor, a dipeptidyl protease inhibitor, insulin (including orally bioavailable insulin preparations), an insulin mimetic, metformin, acarbose, a PPAR-gamma ligand such as troglitazone, rosaglitazone, pioglitazone, or GW-1929, a sulfonylurea, glipazide, glyburide, or chlorpropamide; and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and

c. means for containing said first unit dosage form and said second unit dosage form, wherein the amounts of the first compound and of the second compound result in the desired therapeutic effect of treating diabetes.

Detailed description of preferred embodiments

In one embodiment, the present invention discloses compounds of Formula I, Formula II or Formula III, or a pharmaceutically acceptable derivative thereof, as inhibitors of MCH receptor. The various definitions for the moieties in Formulas I, II and III are given above.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. Thus, for example, the term alkyl (including the alkyl portions of alkoxy) refers to a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a single atom having from 1 to 8 carbon atoms, preferably from 1 to 6;

aryl – represents a carbocyclic group having from 6 to 14 carbon atoms and having at least one benzenoid ring, with all available substitutable aromatic carbon atoms of the carbocyclic group being intended as possible points of attachment. Preferred aryl groups include phenyl, 1-naphthyl, 2-naphthyl and indanyl, and especially phenyl and substituted phenyl;

aralkyl – represents a moiety containing an aryl group linked vial a lower alkyl;

alkylaryl – represents a moiety containing a lower alkyl linked via an aryl group;

cycloalkyl – represents a saturated carbocyclic ring having from 3 to 8 carbon atoms, preferably 5 or 6, optionally substituted.

heterocyclic – represents, in addition to the heteroaryl groups defined below, saturated and unsaturated cyclic organic groups having at least one O, S and/or N atom interrupting a carbocyclic ring structure that consists of one ring or two fused rings, wherein each ring is 5-, 6- or 7-membered and may or may not have double bonds that lack delocalized pi electrons, which ring structure has from 2 to 8,

preferably from 3 to 6 carbon atoms, e.g., 2- or 3-piperidinyl, 2- or 3-piperazinyl, 2- or 3-morpholinyl, or 2- or 3-thiomorpholinyl;

halogen – represents fluorine, chlorine, bromine and iodine;

heteroaryl – represents a cyclic organic group having at least one O, S and/or N atom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclyl group having from 2 to 14, preferably 4 or 5 carbon atoms, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2- or 4-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, or 3- or 4-pyridazinyl, etc.

Representative compounds of the invention which exhibit excellent MCH receptor modulatory activity are listed in **Table I** along with their activity (ranges of K_i values in nanomolar, nM).

Depending upon the structure, the compounds of the invention may form pharmaceutically acceptable salts with organic or inorganic acids, or organic or inorganic bases. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. For formation of salts with bases, suitable bases are, for example, NaOH, KOH, NH_4OH, tetraalkylammonium hydroxide, and the like.

In another embodiment, this invention provides pharmaceutical compositions comprising the above-described inventive aryl or biaryl compounds as an active ingredient. The pharmaceutical compositions generally additionally comprise a pharmaceutically acceptable carrier diluent, excipient or carrier (collectively referred to herein as carrier materials). Because of their MCH inhibitory activity, such pharmaceutical compositions possess utility in treating obesity and related disorders.

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive aryl or biaryl compounds as an active ingredient. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be

administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate. Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. MCH inhibitory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injections or addition of sweeteners and pacifiers for oral solutions,

suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring or similar mixing. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds as well as the pharmaceutical formulations containing the inventive compounds may also be delivered subcutaneously.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 1.0 milligram to about 1,000 milligrams, preferably from about 1.0 to about 950 milligrams, more preferably from about 1.0 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed

may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art.

Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day. The amount and frequency of the administration will be regulated according to the judgment of the attending clinician. A generally recommended daily dosage regimen for oral administration may range from about 1.0 milligram to about 1,000 milligrams per day, in single or divided doses.

Some useful terms are described below:

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gel- refers to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

Powder for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrant - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts

of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glident - material that prevents caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

Another embodiment of the invention discloses the use of the pharmaceutical compositions disclosed above for treatment of diseases such as, for example, obesity and the like. The method comprises administering a therapeutically effective amount of the inventive pharmaceutical composition to a patient having such a disease or diseases and in need of such a treatment.

As stated earlier, the invention also includes tautomers, enantiomers and other stereoisomers of the compounds where applicable. Thus, as one skilled in the art knows, some of the inventive compounds may exist in isomeric forms. Such variations are contemplated to be within the scope of the invention.

Another embodiment of the invention discloses a method of making the inventive aryl or biaryl compounds disclosed herein. The compounds may be prepared by several techniques known in the art. Representative illustrative procedures are outlined in the following reaction schemes.

REACTION SCHEMES

Abbreviations which are used in the descriptions of the schemes, preparations and the examples that follow are:

Abbreviation used:

Ar = argon

Boc = tert-butyloxycarbonyl

tBuOH = tert-butanol

CH_2Cl_2 = dichloromethane

$ClCH_2CH_2Cl$ = 1,2-dichloroethane

CDI = carbonyldiimidazole

DIC = 1,3-dicyclohexylcarbodiimide

DMF = N,N-dimethylformamide

DIEA = N,N-diisopropylethylamine

Et = ethyl

EtOH = ethanol

EtOAc = ethyl acetate

HOBt = 1-hydroxybenzotriazole

H_2SO_4 = sulfuric acid

HCl = hydrogen chloride

H_2O = water

K_2CO_3 = potassium carbonate

LDA = lithium diisopropylamide

LiOH = lithium hydroxide

$LiAlH_4$ = lithium aluminum hydride

Me = methyl

MeI = methyl iodide

MeOH = methanol

Me_2S = dimethylsulfide

NMMO = 4-methylmorpholine N-oxide

$Na(OAc)_3BH$ = sodium triacetoxyborohydride

NaCl = sodium chloride

NaH = sodium hydride

$NaHCO_3$ = sodium bicarbonate

$NaIO_4$ = sodium periodate

Na_2CO_3 = sodium carbonate

NaOH = sodium hydroxide

Na_2SO_4 = sodium sulfate

$Na_2S_2O_3$ = sodium thiosulfate

O_3 = ozone

O_2 = oxygen

OsO_4 = osmium tetroxide

$Pd(PPh_3)_4$ = tetrakis(triphenylphosphine)palladium(0)

$SOCl_2$ = thionyl chloride

TEA = triethylamine

TFA = trifluoroacetic acid

TMSOTf = trimethylsilyl trifluoromethanesulfonate

THF = tetrahydrofuran

HMCHR-CHO = membranes prepared from Chinese hamster ovary cells that overexpress human melanin concentrating hormone.

WGA-SPA beads = Scintillation Assay beads labeled with wheat germ agglutinin

BSA = bovine serum albumin

MCH = melanin concentrating hormone

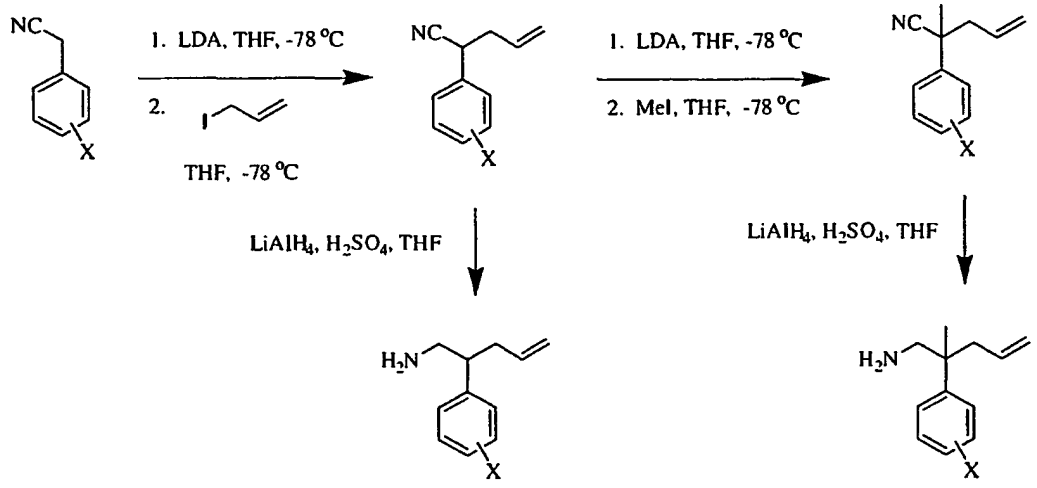
MCHR = melanin concentrating hormone receptor

Several methods for preparing the compounds of this invention and intermediates thereof are illustrated in the following reaction schemes. Starting materials are made using known procedures or as illustrated.

Reaction Schemes 1-2 may be used to synthesize reaction intermediates wherein the structures are aryl amines and aryl carboxylic acids. The synthetic methods used here are modified from known literature procedures, such as: (1) E. D. Edstrom and T. Livinghouse, *J. Am. Chem. Soc.* (1986), 1334-6; (2) C. P. Forbes and G. L. Wenteler, *J. Chem. Soc., Chem. Comm.*, (1986), 279-80; and (3) S. Kano *et al.*, *Chem. Pharm. Bull.*, 1985, 33, 340-6.

In reaction Scheme 1, allylation of the arylacetonitrile may be accomplished using LDA to generate an anion followed by coupling with allyl iodide. The resulting 4-cyano-4-aryl-but-1-ene may be converted to an amine by reduction of the nitrile group by treatment with $LiAlH_4$ to form 5-amino-4-aryl-but-1-ene. Alternatively, the 4-cyano-4-aryl-but-1-ene may be further alkylated, as illustrated using LDA and MeI, to form 4-cyano-4-aryl-4-alkyl-but-1-ene. Reduction of the nitrile group using $LiAlH_4$ affords 5-amino-4-aryl-4-alkyl-but-1-ene.

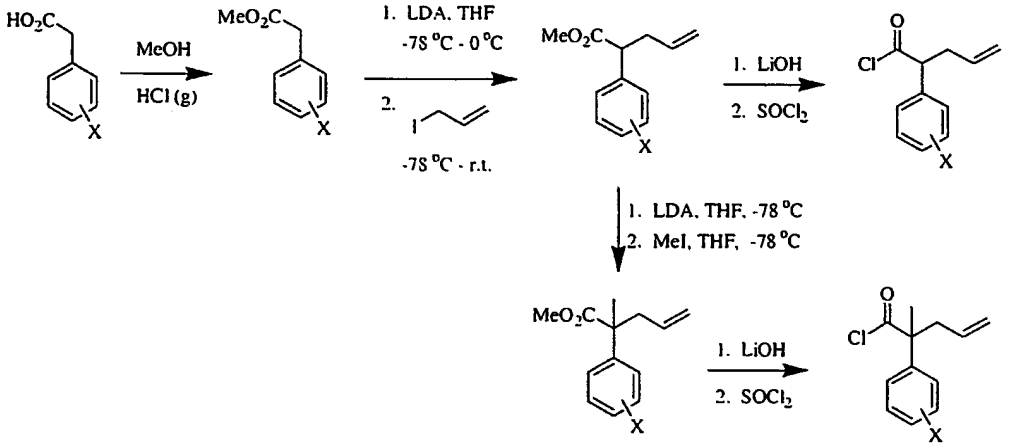
Scheme 1



In reaction Scheme 2, a commercially available aryl acetic acid is first converted to a methyl ester using MeOH/HCl(g). The methyl ester may be allylated using LDA and allyl iodide to form 2-arylpent-4-enoic acid methyl ester. The ester group may be hydrolyzed using a suitable base, such as LiOH in THF/H_2O, to form the carboxylic acid, which can be further converted to the acid chloride using $SOCl_2$.

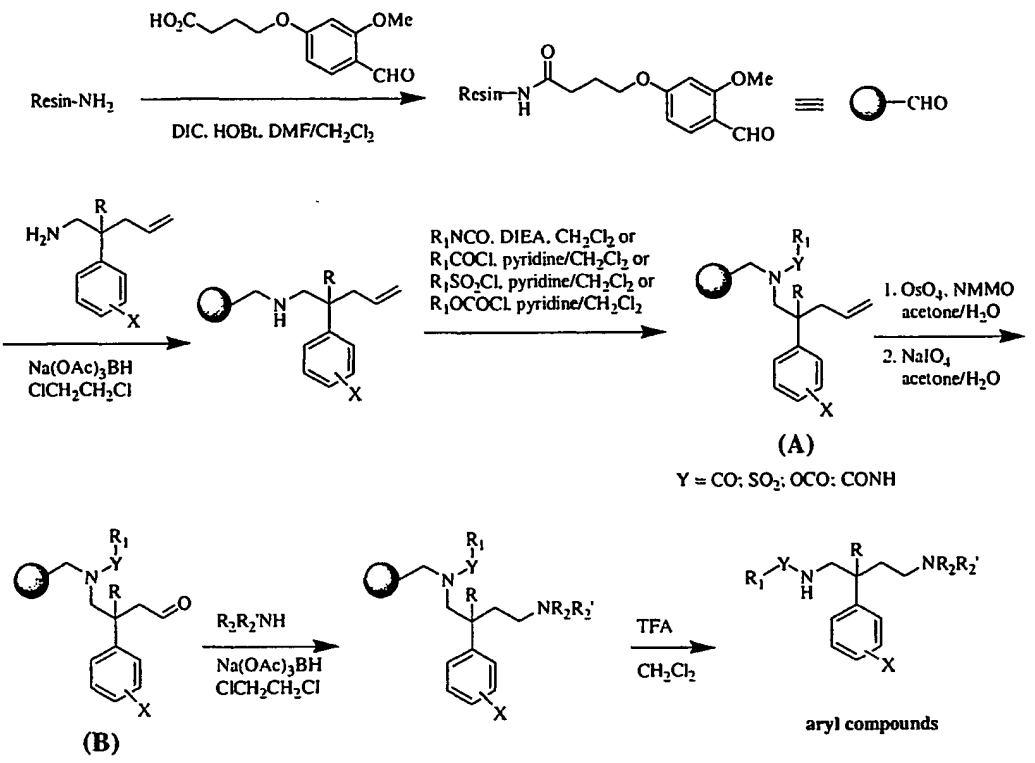
Alternatively, the 2-aryl-pent-4-enoic acid methyl ester may be further alkylated, as illustrated using LDA and MeI, to form 2-aryl-2-alkylpent-4-enoic acid methyl ester. The ester may be then hydrolyzed using a suitable base, such as LiOH in THF/H_2O, to form the corresponding carboxylic acid intermediate, which can be converted to the acid chloride using $SOCl_2$.

Scheme 2



Scheme 3 outlines a general method for preparing compounds of Formula I of the invention using a novel solid phase synthesis method. The synthesis begins with the coupling of a suitable linker, as illustrated using an acid cleavable linker 4-(4-formyl-3-methoxy-phenoxy)-butyric acid, to a suitable amino resin through amide bond formation. Reductive amination of the linker aldehyde with the amine synthon 5-amino-4-aryl-4-R-but-1-ene forms a secondary amine. The secondary amine may be treated with a variety of agents such as an aryl or alkyl isocyanate, acid chloride, sulfonyl chloride, or chloroformate to form the corresponding urea, amide, sulfonamide, or carbamate intermediate A.

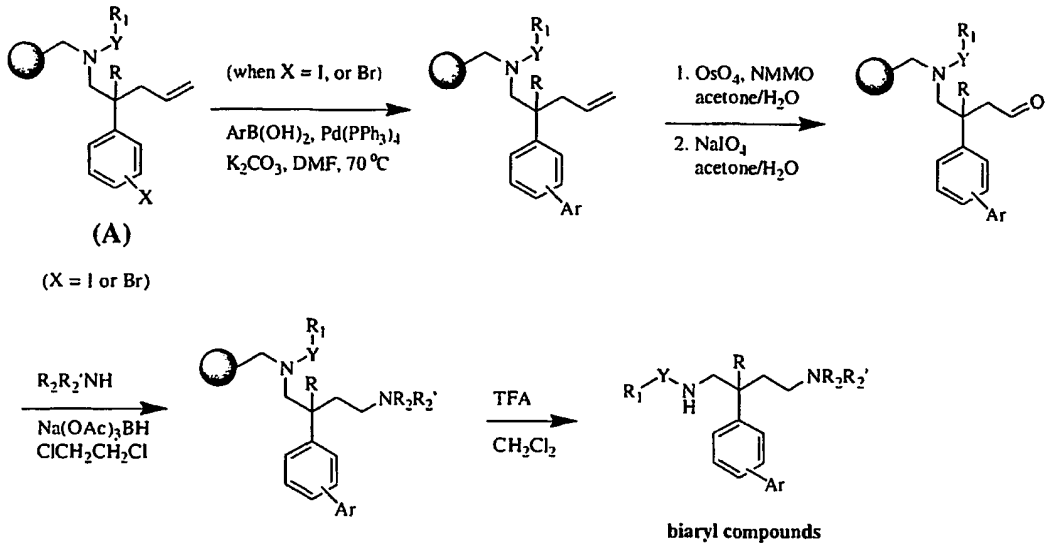
Scheme 3



Intermediate A may be treated with OsO_4/NMMO/$NaIO_4$ to form the aldehyde intermediate B. Intermediate B is able to be converted to a secondary or tertiary amine via reductive amination using a primary or secondary amine and $Na(OAc)_3BH$. The product can be cleaved from the acid labile linker using TFA/CH_2Cl_2 to give the aryl compounds of the invention.

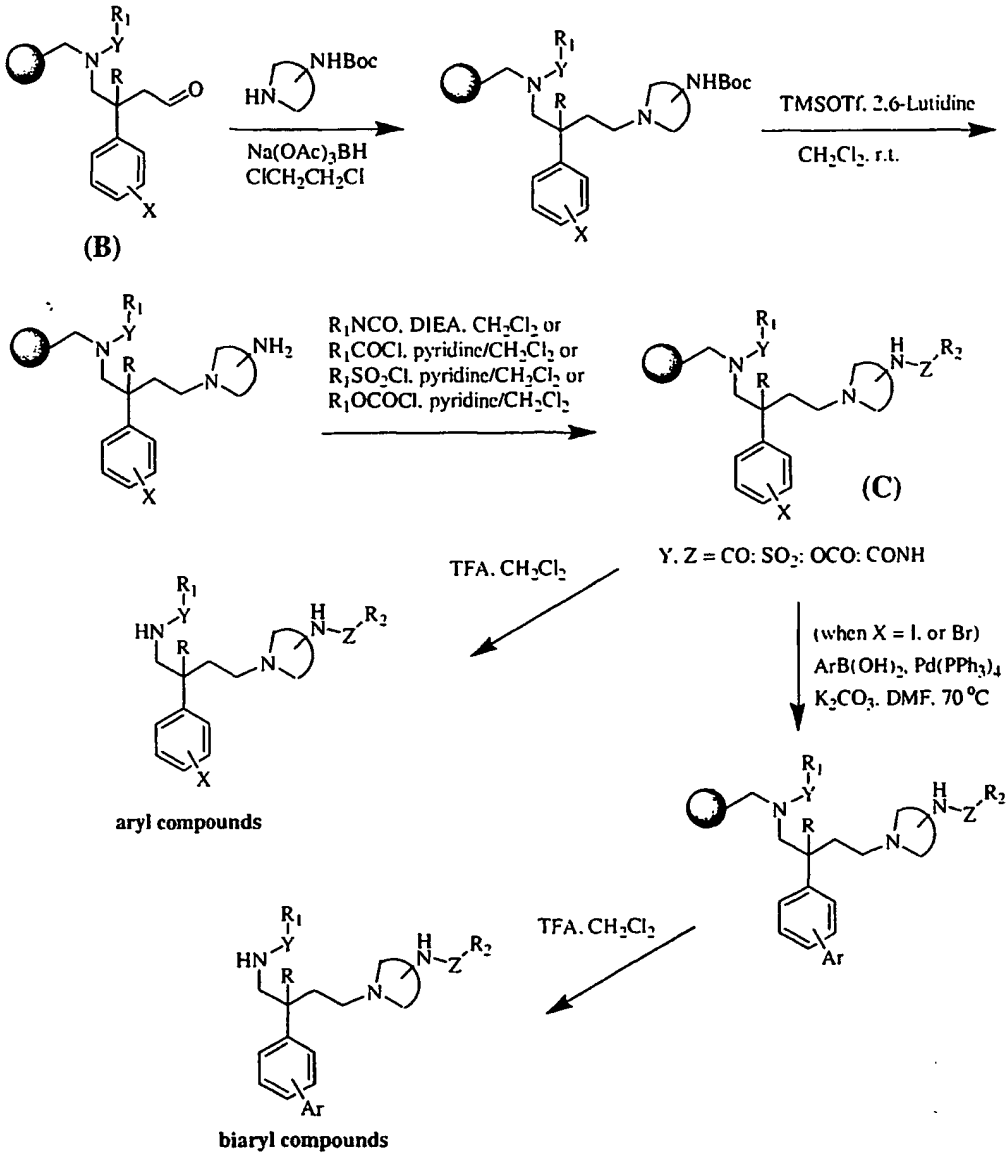
When X = I or Br, intermediate A may be converted to a biaryl compound via Suzuki coupling (A. Suzuki *et al, J. Amer. Chem. Soc.*, 111 (1989) 314). using an arylboronic acid as shown in Scheme 4. The Suzuki coupling product can be treated with OsO_4/NMMO/$NaIO_4$ to convert the terminal olefin group to an aldehyde group. The resulting aldehyde is able to be converted to a secondary or tertiary amine via reductive amination using a primary or secondary amine and $Na(OAc)_3BH$. The final reaction product can be cleaved from the acid labile linker using TFA/CH_2Cl_2 to give the biaryl compounds of the invention.

Scheme 4



Scheme 5 outlines a general method for preparing compounds of Formula I that feature functionalized R_1 groups derived from the intermediate B of Scheme 3. Thus, reductive amination of the aldehyde intermediate B using a Boc-protected diamine, for example, 4-N-*tert*-butyloxycarbonylaminopiperidine, forms a Boc-protected diamine compound. Treatment of the resin with TMSOTf and 2,6-lutidine effects clean removal of the Boc-protecting group with no cleavage of the compound from the acid labile linker (ref.: A. J. Zhang *et al*, *Tet. Lett.* (1998), 39, 7439-7442. The resulting amine can then be derivatized by reacting with an aryl or alkyl isocyanate, acid chloride sulfonyl chloride, or chloroformate to form a corresponding urea, amide, sulfonamide, or carbamate intermediate C, respectively. Intermediate C may be cleaved directly from the acid labile linker using TFA/CH_2Cl_2 to give an aryl compound of Formula I of the invention. Alternatively, intermediate C may be converted to a biaryl compound via Suzuki coupling using an arylboronic acid followed by treatment with TFA/CH_2Cl_2 to give a biaryl compound of Formula I of the invention.

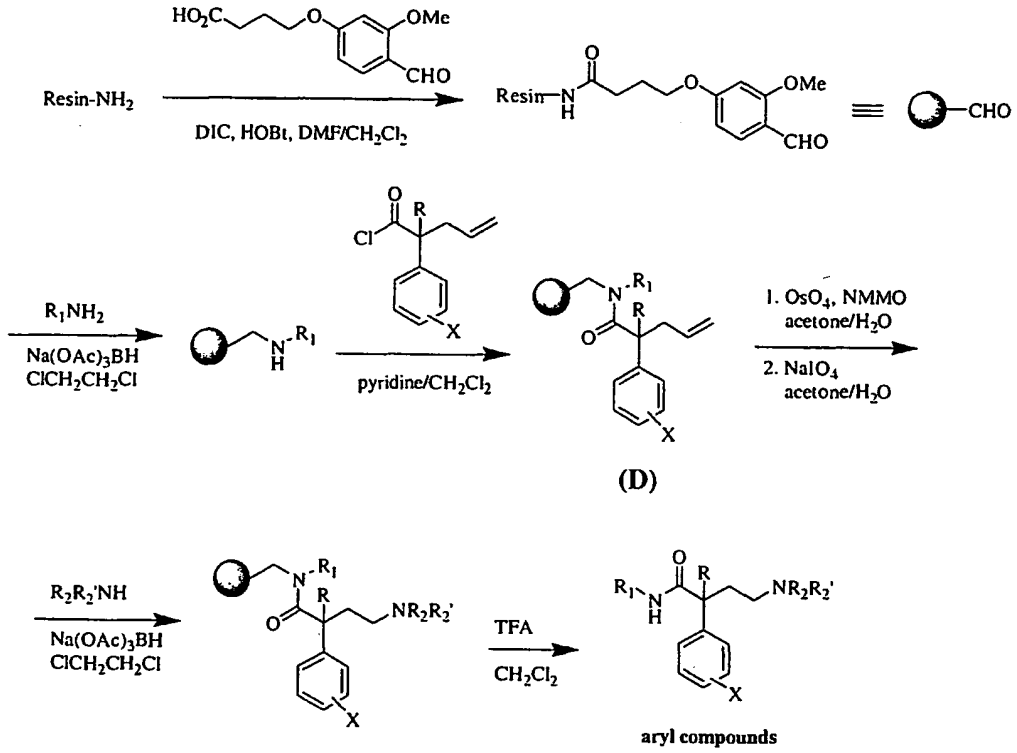
Scheme 5



Scheme 6 outlines a general method for preparing compounds of Formula II of the invention using a novel solid phase synthesis. The synthesis commences with the coupling of a suitable linker, such as illustrated using an acid cleavable linker 4-(4-formyl-3-methoxy-phenoxy)-butyric acid to a suitable amino resin through amide bond formation. Reductive amination of the linker aldehyde with a primary amine forms a resin bound secondary amine. The secondary amine is then coupled with an acid chloride scaffold to form the amide intermediate D. Treatment

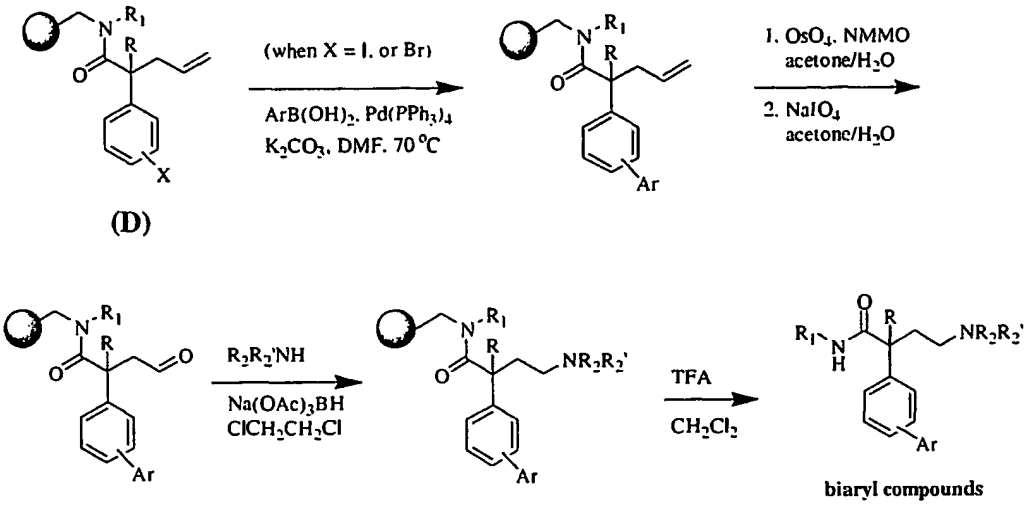
of intermediate D with OsO_4/NMMO/$NaIO_4$ converts the terminal olefin group to an aldehyde group. The aldehyde is able to be converted to a secondary or tertiary amine via reductive amination using a primary or secondary amine and $Na(OAc)_3BH$. Cleavage from the acid labile linker using TFA/CH_2Cl_2 gives an aryl compound of the invention.

Scheme 6



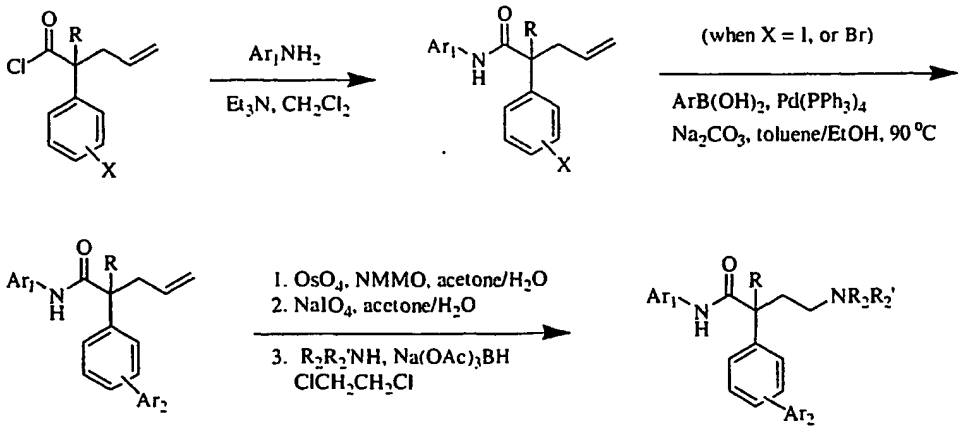
Alternatively, when X = I or Br, intermediate D may be treated with an aryl boronic acid via Suzuki coupling to form a biaryl compound as outlined in Scheme 7. Reaction of the biaryl compound with OsO_4/NMMO/$NaIO_4$ converts the terminal olefin group to an aldehyde group. The resulting aldehyde is able to be converted to a secondary or tertiary amine via reductive amination using a primary or secondary amine and $Na(OAc)_3BH$. Cleaved from the acid labile linker using TFA/CH_2Cl_2 affords a biaryl compound of the invention.

Scheme 7



Scheme 8 illustrates a general solution phase method for preparing compounds of Formula II of the invention. Treatment of an acid chloride scaffold with an aniline gives the amide compound, which can be converted to the biaryl intermediate via Suzuki coupling. Oxidation of the olefin followed by reductive amination provides biaryl compounds of the invention.

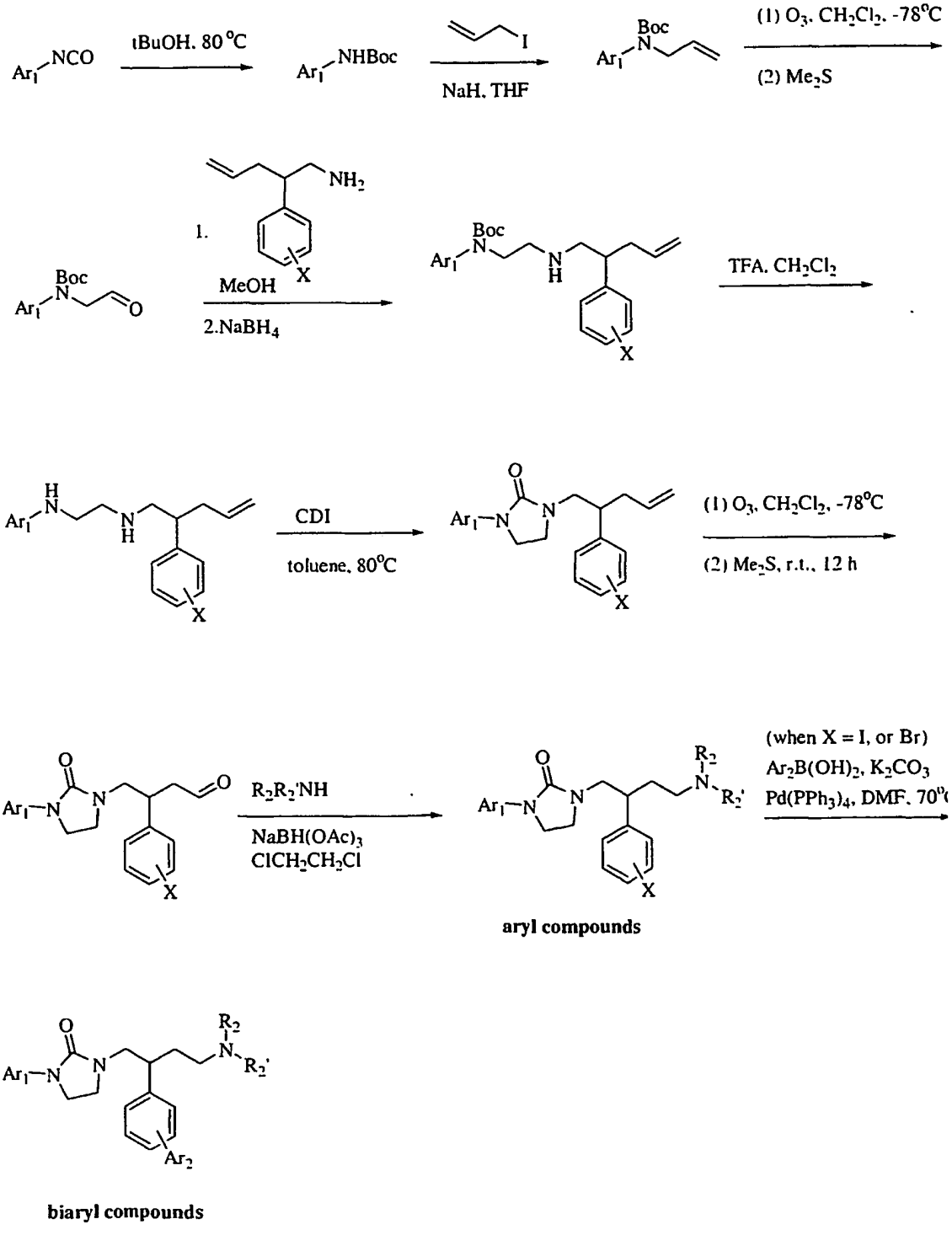
Scheme 8



Scheme 9 outlines a method for preparing the cyclic urea (imidazolidinone) compounds of Formula I of the invention. The synthesis begins with the heating of an aryl isocyanate in *t*-BuOH to form the Boc-protected aniline. Treatment of the

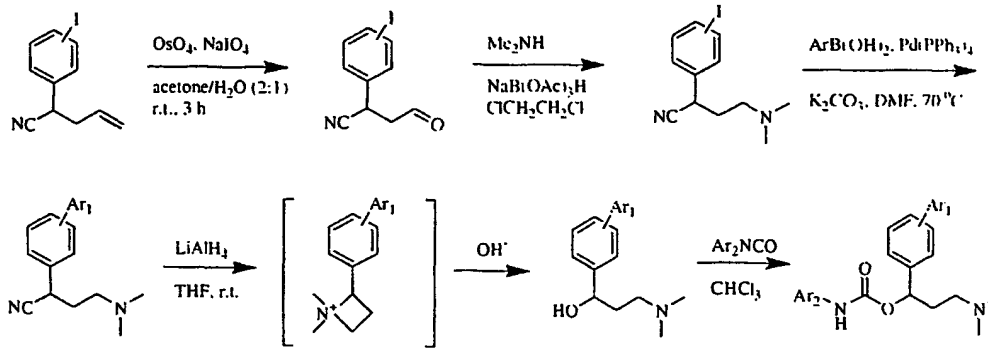
aniline with NaH and allyl iodide yields the Boc-protected N-allyl aniline. The olefin is then converted to an aldehyde via ozonolysis using O_3 followed by Me_2S. The resulting aldehyde is combined with a 5-amino-4-aryl-4-alkyl-but-1-ene synthon through reductive amination to form a secondary amine. The Boc-protecting group on the aniline nitrogen is removed using TFA/CH_2Cl_2 and the resulting diamine is treated with CDI in toluene at reflux to form the cyclic urea intermediate. The olefin group in the cyclic urea intermediate is converted to an aldehyde group via ozonolysis using O_3 followed by Me_2S. Reductive amination of the resulting aldehyde with an appropriate primary or secondary amine provides the cyclic urea aryl compound of Formula I of the invention. When X is an iodo or bromo group, reaction with arylboronic acids under Suzuki coupling conditions gives the cyclic urea biaryl compound of the invention.

Scheme 9


tBuOH. 80 °C
NaH. THF
(1) O3. CH2Cl2. -78°C
(2) Me2S
MeOH
2.NaBH4
TFA. CH2Cl2
CDI
toluene. 80°C
(1) O3. CH2Cl2. -78°C
(2) Me2S. r.t.. 12 h
R2R2'NH
NaBH(OAc)3
ClCH2CH2Cl
(when X = I, or Br)
Ar2B(OH)2. K2CO3
Pd(PPh3)4. DMF. 70°
aryl compounds
biaryl compounds

Scheme 10 outlines a method for preparing the series of carbamate compounds of Formula II of the invention.

Scheme 10

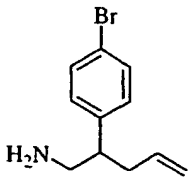


The synthesis starts with the oxidation of an appropriate iodophenylpentenenitrile to form an aldehyde using OsO_4/NMMO/$NaIO_4$. Reductive amination of the aldehyde with an appropriate secondary amine, such as dimethylamine, forms a tertiary amine. Suzuki coupling reaction is then performed to give the biaryl nitrile intermediate. Reduction of the nitrile intermediate using $LiAlH_4$ produced the alcohol product as shown in the scheme, presumably via an azetidinium cation intermediate. Treatment of the alcohol with an aryl isocyanate give the biaryl carbamate compound of Formula II of the invention.

The following Examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention. Examples 1-19 illustrate the synthesis of scaffold intermediates.

EXAMPLE 1

(R,S) 2-(4-Bromophenyl)-pent-4-enylamine (General Procedure)

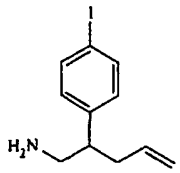
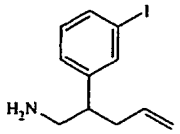
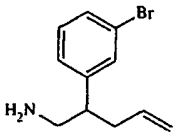
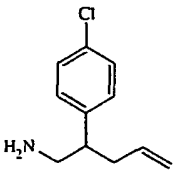
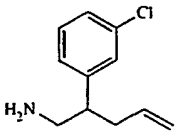
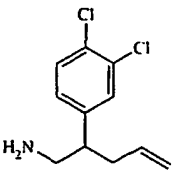


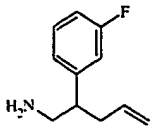
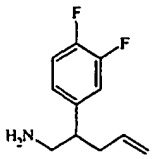
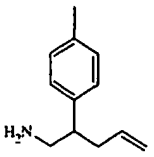
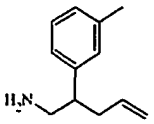
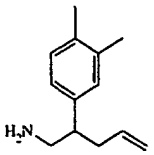
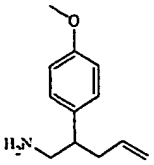
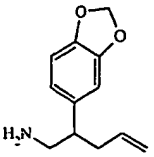
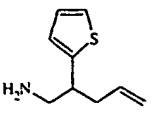
4-Bromophenylacetonitrile (10 g, 52.7 mmol, 1 eq) in THF (100 mL) was cooled to –78 °C under argon. LDA (2 M in THF, 29 mL, 58 mmol, 1.1 eq) was added and the reaction was warmed to 0 °C over 1 h. The reaction was re-cooled

to –78 °C and allyl iodide (6.18 mL, 52.7 mmol, 1 eq) was added and the reaction stirred at –78 °C for a further 2 h. The reaction was diluted with EtOAc (150 mL) and washed with aqueous HCl (1 M, 100 mL), aqueous $Na_2S_2O_3$ (100 mL) and saturated aqueous NaCl (100 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated by rotary evaporation to afford crude 1-cyano-1-(4-bromophenyl)-but-4-ene (10.5 g, ~ 44 mmol) as a yellow oil.

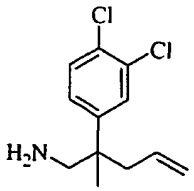
A solution of $LiAlH_4$ (1 M in THF, 123 mL, 123 mmol) in THF (140 mL) was cooled to 0 °C under Ar. H_2SO_4 (95 %, 4 mL, 62.5 mmol) was added in a drop-wise fashion over 10 min. The ice-bath was removed and the mixture was stirred at room temperature for 2 h. A solution of crude 1-cyano-1-(4-bromophenyl)-but-4-ene (10.5 g, ~ 44 mmol) in THF (60 mL) was added in a drop-wise fashion. The reaction was heated to reflux for 1 h, then cooled to room temperature and stirred for 16 h. The reaction was quenched by careful addition of H_2O (4.67 mL, 260 mmol), NaOH (15% aqueous solution, 9.33 mL, 520 mmol) and H_2O (14 mL, 780 mmol). The resulting slurry was diluted with EtOAc and stirred for a further 1 h, then filtered through a pad of celite 545®. The filtered salts were washed with EtOAc (4 x 50 mL) and the filtrate was concentrated by rotary evaporation to afford the title compound 1-amino-2-(4-bromophenyl)-pent-5-ene as a dark brown oil (10.36 g, 43.1 mmol, 88% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$): δ•7.50 (dd, 2H), 7.30 (d, 1H), 7.20 (d, 1H), 5.7 (m, 1H), 5.15 (m, 2H), 3.00 (m, 2H), 2.78 (m, 1H), 2.50 (m, 2H), 1.70 (br s, 2H).

EXAMPLES 2-15 are listed in the following table:

EXAMPLE	STRUCTURE	^{1}H-NMR (300 MHz, $CDCl_3$)
2		7.75 (d, 2H), 7.05 (d, 2H), 5.75 (m, 1H), 5.11 (m, 2H), 3.08 (m, 1H), 2.95 (m, 1H), 2.79 (m, 1H), 2.46 (m, 2H), 2.04 (br.s, 2H).
3		7.66 (m, 2H), 7.38 (m, 1H), 7.18 (m, 1H), 5.77 (m, 1H), 5.12 (m, 2H), 3.02 (m, 2H), 2.75 (m, 1H), 2.49 (m, 2H), 1.56 (br.s, 2H).
4		7.30 (m, 4H), 5.78 (m, 1 H), 5.10 (m, 2H), 3.09 (m, 1H), 2.95 (m, 1H), 2.80 (m, 1H), 2.49 (m, 2H), 2.80 (m, 1H), 2.49 (m, 2H), 1.80 (br.s, 2 H).
5		7.23 (d, 2H), 7.11 (d, 2H), 5.61 (m, 1H), 4.98 (m, 2H), 2.90 (m, 2H), 2.70 (m, 1H), 2.33 (m, 2H), 1.82 (br.s, 2H).
6		7.33 (m, 3H), 7.17 (m, 1H), 5.77 (m, 1H), 5.11 (m, 2H), 3.08 (m, 1H), 2.96 (m, 1H), 2.79 (m, 1H), 2.49 (m, 2H), 1.43 (br.s, 2H).
7		7.51 (dd, 1H), 7.39 (dd, 1H), 7.15 (dd, 1H), 5.75 (m, 1H), 5.11 (m, 2H), 3.08 (m, 1H), 2.95 (m, 1H), 2.78 (m, 1H), 2.48 (m, 2H), 1.68 (br.s, 2H).

EXAMPLE	STRUCTURE	^{1}H-NMR (300 MHz, $CDCl_3$)
8		7.38 (m. 1H). 7.05 (m. 3H). 5.77 (m. 1H). 5.11 (m. 2H). 3.02 (m. 2H). 2.81 (m. 1H). 2.48 (m. 2H). 1.50 (br.s. 2H).
9		7.14 (m. 3H). 5.72 (m. 1H). 5.08 (m. 2H). 3.06 (dd. 1H). 2.92 (dd. 1H). 2.78 (m. 1H). 2.46 (m. 2H). 1.70 (br.s. 2H).
10		7.22 (dd. 4H). 5.80 (m. 1H). 5.11 (m. 2H). 3.07 (m. 1H). 2.95 (m. 1H). 2.79 (m. 1H). 2.50 (m. 2H). 2.45 (s. 3H). 1.58 (br.s. 2H).
11		7.32 (m. 1H). 7.12 (m. 3H). 5.81 (m. 1H). 5.12 (m. 2H). 3.06 (m. 1H). 2.96 (m. 1H). 2.77 (m. 1H). 2.48 (m. 2H). 2.47 (s. 3H). 1.62 (br.s. 2H).
12		7.21 (m. 1H). 7.06 (m. 2H). 5.81 (m. 1H). 5.10 (m. 2H). 3.07 (m. 1H). 2.94 (m. 1H). 2.76 (m. 1H). 2.48 (m. 2H). 2.36 (s. 3H). 2.34(s. 3H). 1.73 (br.s. 2H).
13		7.22 (d. 2H). 6.98 (d. 2H). 5.8 (m. 1H). 5.10 (m. 2H). 3.89 (s. 3H). 2.98 (m. 2H). 2.76 (m. 1H). 2.48 (m. 2H). 1.43 (br.s. 2H).
14		6.80 (m. 3H). 6.20 (s. 2H). 5.79 (m. 1H). 5.08 (m. 2H). 3.02 (m. 1H). 2.88 (m. 1H). 2.74 (m. 1H). 2.41 (m. 2H). 1.88 (br.s. 2H).
15		7.29 (m. 1H). 7.08 (m. 1H). 6.96 (m. 1H). 5.84 (m. 1H). 5.16 (m. 2H). 3.16 (m. 1H). 3.12 (m. 2H). 2.57 (m. 2H). 1.66 (br.s. 2H).

EXAMPLE 16: 2-(3,4-Dichlorophenyl)-2-methyl-pent-4-enylamine:



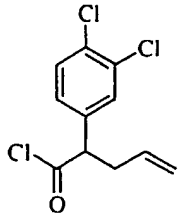
3,4-Dichlorophenylacetonitrile (5 g, 26.87 mmol, 1 eq) in THF (50 mL) was cooled to -78 °C under Ar. LDA (2 M in THF, 16.1 mL, 32.2 mmol, 1.2 eq) was added and the reaction was warmed to 0 °C over 1 h. The reaction was re-cooled to –78 °C and allyl iodide (2.67 mL, 26.87 mmol, 1 eq) was added then the reaction was stirred at –78 °C for a further 2 h. The reaction was diluted with EtOAc (150 mL) and washed with aqueous HCl (1 M, 100 mL), saturated aqueous $Na_2S_2O_3$ (100 mL) and saturated aqueous NaCl (100 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated by rotary evaporation to afford 2-(3,4-dichlorophenyl)-pent-4-enenitrile (6.3 g, ~ 28 mmol) as a yellow oil.

A 1 g (4.4 mmol) portion of 2-(3,4-dichlorophenyl)-pent-4-enenitrile in THF (25 mL) at –78 °C under Ar was treated with LDA (2M in THF, 2.7 mL, 5.4 mmol, 1.2 eq). The reaction was warmed to 0 °C for 1 h, then re-cooled to –78 °C and methyl iodide (0.28 mL, 4.4 mmol, 1.0 eq) was added. The reaction was stirred at –78 °C for 1 h, then diluted with EtOAc and washed with aqueous HCl (1 M, 25 mL), aqueous $Na_2S_2O_3$ (25 mL) and saturated aqueous NaCl (25 mL). The organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to afford 2-(3,4-dichlorophenyl)-2-methyl-pent-4-enenitrile (1.04 g, 4.39 mmol, 99.8%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$):δ 7.60 (dd, 1H), 7.35 (m, 2H), 5.77 (m, 1H), 5.28 (m, 2H), 2.72 (m, 2H), 1.8 (s, 3H).

A solution of $LiAlH_4$ (1 M in THF, 18.65 mL, 18.65 mmol,) in THF (25 mL) was cooled to 0 °C under Ar. H_2SO_4 (95 %, 0.51 mL, 9.38 mmol) was added in a drop-wise fashion over 10 min. The mixture was stirred at room temperature for 2 h, then a solution of 2-(3,4-dichlorophenyl)-2-methyl-pent-4-enenitrile (1.28 g, 6.22

mmol) in THF (10 mL) was added in a drop-wise fashion. The reaction was heated to reflux for 1 h, then cooled to room temperature and stirred for 16 h. The reaction was quenched by careful addition of H_2O (0.71 mL, 12.8 mmol), NaOH (15% aqueous solution, 1.34 mL, 25.6 mmol) and H_2O (2.05 mL, 38.4 mmol). The resulting slurry was stirred for a further 1 h and then filtered through a pad of celite 545®. The filtered salts were washed with EtOAc (4 x 20 mL) and the combined organic filtrate was concentrated by rotary evaporation to afford the title compound 1-amino- 2-(3,4-dichlorophenyl)-2-methyl-pent-4-enylamine (1.22g, 4.99 mmol, 80.2%) as a dark brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (m,1H), 7.25 (m, 2H), 5.63 (m, 1H), 5.10 (m, 2H), 2.94 (dd, 2H), 2.54 (m, 2H), 2.03 (br s, NH_2), 1.4 (s, 3H).

EXAMPLE 17: (R,S)-2-(3,4-Dichloro-phenyl)-pent-4-enoyl Chloride:



A solution of (3,4-dichloro-phenyl)-acetic acid (16.12 g, 78.5 mmol) in MeOH (500 mL) was bubbled with HCl gas for 5 min. The mixture was stirred at room temperature for 1 h. The solvent was removed by rotary evaporation and the resulting residue was dissolved in EtOAc (400 mL) and washed with saturated aqueous $NaHCO_3$ (200 mL) and saturated aqueous NaCl (200 mL). The organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to give (3,4-dichloro-phenyl)-acetic acid methyl ester (16.22 g, 74.1 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (m, 2H), 7.23 (dd, 1H), 3.81 (s, 3H), 3.69 (s, 2H).

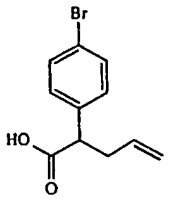
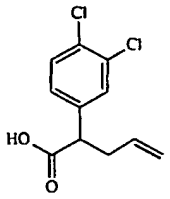
(3,4-Dichloro-phenyl)-acetic acid methyl ester (5 g, 22.8 mmol) in THF (50 mL) was cooled to –78 °C under Ar. LDA (2M in THF, 13.7 mL, 27.4 mmol, 1.2 eq) was added in a drop-wise fashion and then the reaction was warmed to 0 °C for 1 h. The reaction was cooled to –78 °C and allyl iodide (2.1 mL, 22.8 mmol, 1 eq) was added. The reaction was stirred at –78 °C for 4 h and then diluted with EtOAc

(200 mL), washed with saturated aqueous $Na_2S_2O_3$ (100 mL) and saturated aqueous NaCl (100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated by rotary evaporation to give crude (R,S)-2-(3,4-dichloro-phenyl)-pent-4-enoic acid methyl ester (6.0 g, ~22 mmol, 100%) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (m, 2H), 7.26 (dd, 1H), 5.78 (m, 1H), 5.15 (m, 2H), 3.79 (s, 1H), 3.71 (m, 1H), 2.90 (m,1H), 2.60 (m, 1H).

Lithium hydroxide (1.66 g, 69.3 mmol, 3 eq) was dissolved in H_2O (50 mL) and added to a solution of (R,S)-2-(3,4-dichloro-phenyl)-pent-4-enoic acid methyl ester (6 g, 22 mmol) dissolved in THF/MeOH (1.5:1 v:v, 250 mL) and the resulting mixture was stirred at room temperature for 3 h. The solvent was removed by rotary evaporation and the residue was partitioned between EtOAc and H_2O. The aqueous layer was acidified to pH 3 with aqueous 6N HCl and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL) and concentrated by rotary evaporation to give (R,S)-2-(3,4-dichloro-phenyl)-pent-4-enoic acid as a brown solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.52(m, 2H), 7.28(dd, 1H), 5.79(m, 1H), 5.17(m, 2H), 3.73(t, 1H), 2.91(m, 1H), 2.62(m, 1H).

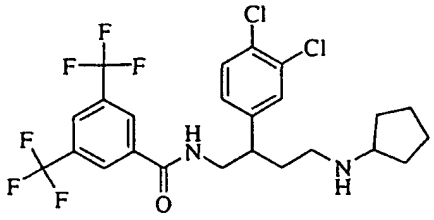
(R,S)-2-(3,4-Dichloro-phenyl)-pent-4-enoic acid (2.5 g, 10.24 mmol, 1 eq) was dissolved in $SOCl_2$ (10 mL). The reaction mixture was heated to reflux for 1 h and then the $SOCl_2$ was removed by rotary evaporation. The residue was co-evaporated from toluene (3 x 5 mL) and then dried under high vacuum for 1 h. It was re-dissolved in toluene (1 mL) and concentrated by rotary evaporation and then dried under high vacuum for 4 h to give the title compound (R,S)-2-(3,4-dichloro-phenyl)-pent-4-enoyl chloride (2.69 g, 10.2 mmol, ~100%). The acid chloride was used directly in the solid phase synthesis reactions.

EXAMPLES 18-19 are listed in the following table:

EXAMPLE	STRUCTURE	^{1}H-NMR (300 MHz, $CDCl_3$)
18		7.58 (d, 2H), 7.32 (d, 2H), 5.81 (m, 1H), 5.16 (m, 2H), 3.73 (dd, 1H), 2.90 (m, 1H), 2.63 (m, 1H).
19		7.52 (m, 2H), 7.28 (dd, 1H), 5.79 (m, 1H), 5.17 (m, 2H), 3.73 (t, 1H), 2.91 (m, 1H), 2.62 (m, 1H).

Examples 20-33 illustrate the synthesis of MCH active compounds.

EXAMPLE 20 (R,S)-N-[4-Cyclopentylamino-2-(3,4-dichloro-phenyl)-butyl]-3,5-bis-trifluoromethyl-benzamide:



A 1 liter bottle was charged with ArgoGel-NH_2 (30 g, 12 mmol, supplied by Argonaut Technologies, Incorporated, California), CH_2Cl_2 (200 mL) and DMF (50 mL). A pre-mixed (30 min) solution of 4-(4-formyl-3-methoxy-phenoxy)-butyric acid linker (8.577 g, 36 mmol, 3 eq), HOBt (4.865 g, 36 mmol, 3 eq) and DIC (11.54 mL, 72 mmol, 6 eq) in CH_2Cl_2 (250 mL) was added to the resin suspension and the mixture was shaken at room temperature for 16 h. The resin was transferred to 2 large shaking vessels, the solution was drained and the resin was washed with DMF (3X), MeOH (3X) and CH_2Cl_2 (3X) and dried under high vacuum to give the acid cleavable linker containing 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin.

A 100 mg (0.04 mmol) portion of the resin was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(3,4-dichlorophenyl)-pent-5-ene (0.05 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(OAc)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added and the reaction was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

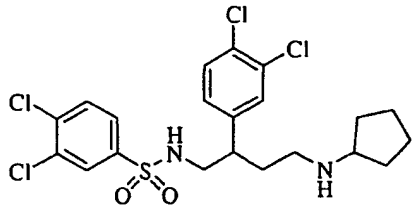
The resin was suspended in pyridine (1.5 mL) and 3,5-bis(trifluoromethyl)benzoyl chloride (1.5 mL of a 1 M solution in CH_2Cl_2, 1.5 mmol) was added. The resin was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X) and acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of cyclopentylamine (0.024 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05 g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive chloranil test. The resin was treated with a solution of TFA (25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90%

acetonitrile/water) to yield the title compound (0.0050 g, 27%), MS (ESI): 541.1 (M+1), 543.1 (M+3).

EXAMPLE 21 (R,S)-3,4-Dichloro-N-[4-cyclopentylamino-2-(3,4-dichloro-phenyl)-butyl]-benzenesulfonamide:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(3,4-dichlorophenyl)-pent-5-ene (0.05 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(OAc)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added. The reaction was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

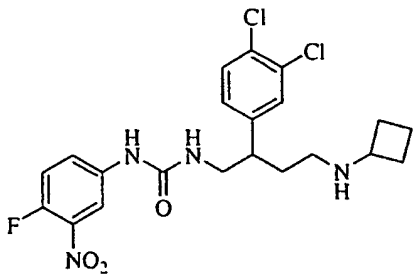
The resin was suspended in pyridine (1.5 mL) and 3,4-dichlorobenzenesulfonyl chloride (1.5 mL of a 1 M solution in CH_2Cl_2, 1.5 mmol) was added. The resin was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O

(1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of cyclopentylamine (0.024 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive chloranil test. The resin was treated with a solution of TFA (TFA, 25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield the title compound (0.00102 g, 47%). MS (ESI): 509.1 (M+1), 511.0 (M+3), 513.0 (M+5).

EXAMPLE 22 (R,S)-[3-Cyclobutylamino-2-(3,4-dichloro-phenyl)-propyl]-3-(4-fluoro-3-nitro-phenyl)-urea:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(3,4-dichlorophenyl)-pent-5-ene (0.047 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(OAc)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added. The reaction was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

The resin was suspended in CH_2Cl_2 (3.0 mL) and DIEA (0.035 mL, 5 eq) was added, followed by 3-nitro-4-fluorophenyl isocyanate (0.217 mL, 1.5 mmol). The

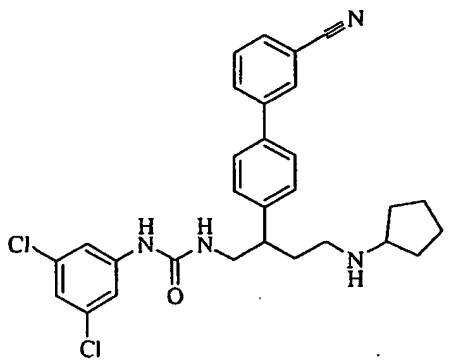
mixture was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of cyclobutylamine hydrochloride (0.022 g, 0.2 mmol, 5 eq) and triethylamine (0.03 mL, 0.2 mmol) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05 g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive chloranil test. The resin was treated with a solution of TFA (25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield the title compound (0.0062 g, 33%). MS (ESI): 469.0 (M+1), 471.0 (M+3).

EXAMPLE 23

(R,S)-1-[2-(3'-Cyano-biphenyl-4-yl)-4-cyclopentylamino-butyl]-3-(3,5-dichloro-phenyl)-urea:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(4-bromophenyl)-pent-5-ene (0.048 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(OAc)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added. The reaction was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

The resin was suspended in CH_2Cl_2 (3.0 mL) and DIEA (0.035 mL, 0.2 mmol, 5 eq) was added, followed by 3,5-dichlorophenyl isocyanate (0.283 g, 1.5 mmol, to give a 0.5M solution). The mixture was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

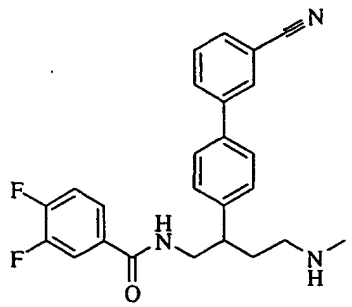
The resin was mixed with 3-cyanophenylboronic acid (0.024 g, 0.16 mmol, 4 eq), K_2CO_3 (0.028 g, 0.2 mmol, 5 eq) and $Pd(PPh_3)_4$ (0.009 g, 0.008 mmol, 0.2 eq). DMF (2 mL, degassed with Ar) was added and the mixture was heated to 70 °C for 16 h. The solution was filtered and the resin washed with DMF (4X), H_2O (4X), MeOH (3X) and CH_2Cl_2 (4X).

The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of cyclopentylamine (0.02 mL, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(Oac)_3BH$ (0.05 g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive chloranil test. The resin was treated with a solution of TFA (25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield (R,S)-1-[2-(3'-Cyano-biphenyl-4-yl)-4-cyclopentylamino-butyl]-3-(3,5-dichloro-phenyl)-urea (0.092 g, 44%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 2H), 7.51 (m, 1H), 7.44 (m, 3H), 7.24 (m, 4H), 6.80 (dd, 1H), 3.26 (m, 3H), 2.84 (m, 1H), 2.65 (m, 2H), 2.05 (m, 1H), 1.88 (m, 3H), 1.65 (m, 2H), 1.47 (m, 3H); MS (ESI): 521.0 (M+1), 523.0 (M+3).

EXAMPLE 24

(R,S)-N-[2-(3'-Cyano-biphenyl-4-yl)-4-methylamino-butyl]-3,4-difluoro-benzamide:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(4-iodophenyl)-pent-5-ene (0.05 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(Oac)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added. The reaction was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An

aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

The resin was suspended in pyridine (1.5 mL) and 3,4-difluorobenzoyl chloride (1.5 mL of a 1 M solution in CH_2Cl_2, 1.5 mmol) was added. The resin was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

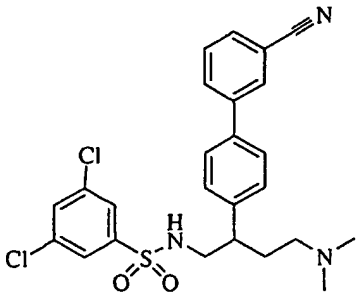
To the resin was added 3-cyanophenylboronic acid (0.024 g, 0.16 mmol, 4 eq), K_2CO_3 (0.028 g, 0.2 mmol, 5 eq) and $Pd(PPh_3)_4$ (0.009 g, 0.008 mmol, 0.2 eq). DMF (2 mL, degassed with Ar) was added and the mixture was heated to 70 °C for 16 h. The solution was filtered and the resin washed with DMF (4X), H_2O (4X), MeOH (3X) and CH_2Cl_2 (4X).

The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of methylamine (0.21 mL, 2M solution, 0.4 mmol, 10 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05 g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive chloranil test. The resin was treated with a solution of TFA (25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield the title compound (0.0019 g, 11%). MS (ESI): 420.1 (M+1), 421.1 (M+2).

EXAMPLE 25

(R,S)-3,5-Dichloro-N-[2-(3'-cyano-biphenyl-4-yl)-4-dimethylamino-butyl]-benzenesulfonamide:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(4-iodophenyl)-pent-5-ene (0.05 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(OAc)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added. The reaction was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

The resin was suspended in pyridine (1.5 mL) and 3,5-dichlorobenzenesulfonyl chloride (1.5 mL of a 1 M solution in CH_2Cl_2, 1.5 mmol) was added. The resin was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

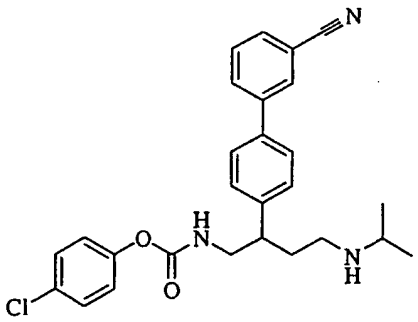
The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq)

in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of dimethylamine (0.10 mL of a 2 M solution in THF, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive chloranil test. The resin was treated with a solution of TFA (TFA, 25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield the title compound (0.0024 g, 12%). MS (ESI): 502.1/504.1 (M+1).

EXAMPLE 26

(R,S)- [2-(3'-Cyano-biphenyl-4-yl)-4-isopropylamino-butyl]-carbamic acid 4-chloro-phenyl ester:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(4-iodophenyl)-pent-5-ene (0.05 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(OAc)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added. The reaction was shaken at room temperature for 16 h. The solution was filtered and

the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

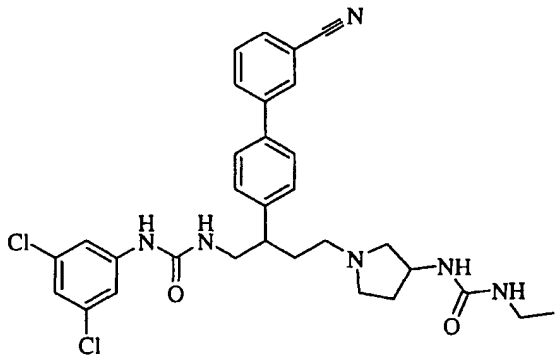
The resin was suspended in pyridine (1.5 mL) and 4-chlorophenyl chloroformate (1.5 mL of a 1 M solution in CH_2Cl_2, 1.5 mmol) was added. The resin was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of isopropylamine (0.02 mL , 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive chloranil test. The resin was treated with a solution of TFA (TFA, 25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield the title compound (0.0027 g, 15%). MS (ESI): 460.1/462.2 (M+1).

EXAMPLE 27

(R,S)-1-(1-{3-(3'-Cyano-biphenyl-4-yl)-4-[3-(3,5-dichloro-phenyl)-ureido]-butyl}-pyrrolidin-3-yl)-3-ethyl-urea:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(4-bromophenyl)-pent-5-ene (0.048 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(OAc)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added. The reaction was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

The resin was suspended in CH_2Cl_2 (3.0 mL) and DIEA (0.035 mL, 0.2 mmol, 5 eq) was added followed by 3,5-dichlorophenyl isocyanate (10.283 g, 1.5 mmol, to give a 0.5 M solution). The resin was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

To the resin was added 3-cyanophenylboronic acid (0.024 g, 0.16 mmol, 4 eq), K_2CO_3 (0.028 g, 0.2 mmol, 5 eq) and $Pd(PPh_3)_4$ (0.009 g, 0.008 mmol, 0.2 eq). DMF (2 mL, degassed with Ar) was added and the mixture was heated to 70 °C for 16 h. The solution was filtered and the resin washed with DMF (4X), H_2O (4X), MeOH (3X) and CH_2Cl_2 (4X).

The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of pyrrolidin-3-yl-carbamic acid tert-butyl ester (0.037 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05 g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X).

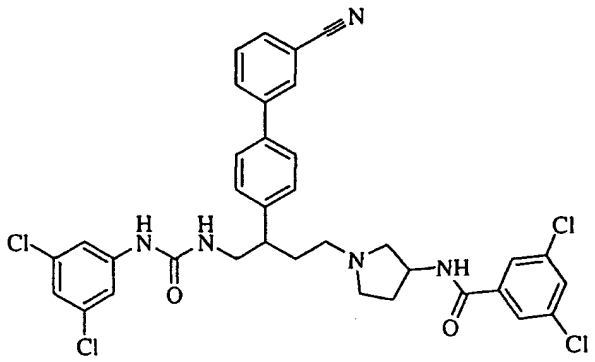
The resin was suspended in CH_2Cl_2 (3 mL) and treated with 2,6-lutidine (0.52 mL, 4.5 mmol, 1.5M final concentration) and TMSOTf (0.54 mL, 3 mmol, 1M final concentration). The mixture was shaken at room temperature for 1 h. The mixture was drained and the resin washed with CH_2Cl_2 (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive ninhydrin test.

The resin was suspended in CH_2Cl_2 (3 mL) and treated with ethyl isocyanate (0.19 mL, 1.5 mmol, 0.5M final concentration) and DIEA (0.035 mL, 0.2 mmol, 5 eq). The mixture was shaken at room temperature for 14 h and then the solution was filtered and the resin was washed with DMF (3X), MeOH (3X) and CH_2Cl_2 (3X).

The resin was treated with a solution of TFA (25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield the title compound (0.0011 g, 5%). MS(ESI): 593.1 (M+1), 595.1 (M+3).

EXAMPLE 28

(R,S)-3,5-Dichloro-N-(1-{3-(3'-cyano-biphenyl-4-yl)-4-[3-(3,5-dichloro-phenyl)-ureido]-butyl}-pyrrolidin-3-yl)-benzamide:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(4-bromophenyl)-pent-5-ene (0.048 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(OAc)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added. The reaction was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

The resin was suspended in CH_2Cl_2 (3.0 mL) and DIEA (0.035 mL, 0.2 mmol, 5 eq) was added followed by 3,5-dichlorophenyl isocyanate (10.283 g, 1.5 mmol, to give a 0.5 M solution). The resin was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

To the resin was added 3-cyanophenylboronic acid (0.024 g, 0.16 mmol, 4 eq), K_2CO_3 (0.028 g, 0.2 mmol, 5 eq) and $Pd(PPh_3)_4$ (0.009 g, 0.008 mmol, 0.2 eq). DMF (2 mL, degassed with Ar) was added and the mixture was heated to 70 °C for 16 h. The solution was filtered and the resin washed with DMF (4X), H_2O (4X), MeOH (3X) and CH_2Cl_2 (4X).

The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq)

in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of pyrrolidin-3-yl-carbamic acid tert-butyl ester (0.037 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05 g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X).

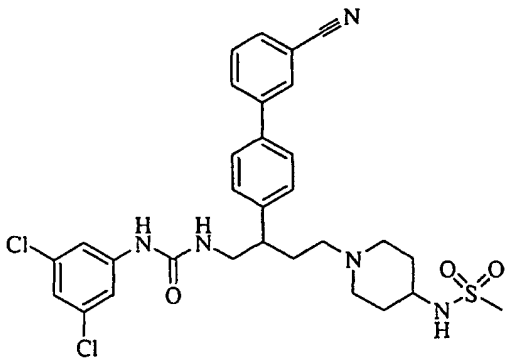
The resin was suspended in CH_2Cl_2 (3 mL) and treated with 2,6-lutidine (0.52 mL, 4.5 mmol, 1.5M final concentration) and TMSOTf (0.54 mL, 3 mmol, 1M final concentration). The mixture was shaken at room temperature for 1 h. The mixture was drained and the resin washed with CH_2Cl_2 (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive ninhydrin test.

The resin was suspended in CH_2Cl_2 (1.5 mL) and treated with 3,5-dichlorobenzoyl chloride (0.315 g, 1.5 mmol) and pyridine (1.5 mL). The mixture was shaken at room temperature for 14 h and then the solution was filtered and the resin was washed with DMF (3X), MeOH (3X) and CH_2Cl_2 (3X).

The resin was treated with a solution of TFA (25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield the title compound (0.0023 g, 9%). MS(ESI): 693.9/695.9/697.9 (M+1).

EXAMPLE 29

(R,S)-N-(1-{3-(3'-Cyano-biphenyl-4-yl)-4-[3-(3,5-dichloro-phenyl)-ureido]-butyl}-piperidin-4-yl)-methanesulfonamide:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 1-amino-2-(4-bromophenyl)-pent-5-ene (0.048 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $Na(OAc)_3BH$ (0.045 g, 0.2 mmol, 5 eq) was added. The reaction was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

The resin was suspended in CH_2Cl_2 (3.0 mL) and DIEA (0.035 mL, 0.2 mmol, eq) was added followed by 3,5-dichlorophenyl isocyanate (0.283g, 1.5 mmol, to give a 0.5 M solution). The resin was shaken at room temperature for 16 h, the solution filtered and the resin washed with CH_2Cl_2 (3X), DMF (3X), MeOH (2X) and CH_2Cl_2 (3X). An aliquot of the resin gave a negative chloranil test.

The resin was added 3-cyanophenylboronic acid (0.024 g, 0.16 mmol, 4 eq), K_2CO_3 (0.028 m, 0.2 mmol, 5 eq) and $Pd(PPh_3)_4$ (0.009 g, 0.008 mmol, 0.2 eq). DMF (2 mL, degassed with Ar) was added and the mixture was heated to 70 °C for 16 h. The solution was filtered and the resin washed with DMF (4X), H_2O (4X), MeOH (3X) and CH_2Cl_2 (4X).

The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of piperidin-4-yl-carbamic acid tert-butyl ester (0.043 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05 g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X).

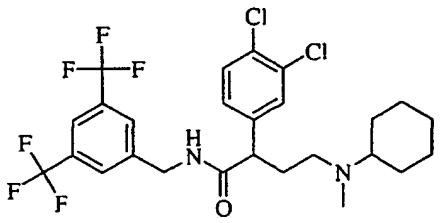
The resin was suspended in CH_2Cl_2 (3 mL) and treated with 2,6-lutidine (0.52 mL, 4.5 mmol, 1.5M final concentration) and TMSOTf (0.54 mL, 3 mmol, 1M final concentration). The mixture was shaken at room temperature for 1 h. The solution was filtered and the resin was washed with CH_2Cl_2 (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive ninhydrin test.

The resin was suspended in pyridine (1.5 mL) and treated with methanesulfonyl chloride (1.5 mL of a 1.0M solution in CH_2Cl_2). The mixture was shaken at room temperature for 14 h. The solution was filtered and the resin was washed DMF (3X), MeOH (3X) and CH_2Cl_2 (3X).

The resin was treated with a solution of TFA (25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield the title compound (0.0012 g, 5%). MS (ESI): 614.1 (M+1), 616.1(M+3).

EXAMPLE 30

(R,S)-N-(3,5-Bis-trifluoromethyl-benzyl)-4-(cyclohexyl-methyl-amino)-2-(3,4-dichloro-phenyl)-butyramide:



A 100 mg (0.04 mmol) portion of the 4-(4-formyl-3-methoxy-phenoxy)-butyramide resin (see step 1 of EXAMPLE 20) was suspended in $ClCH_2CH_2Cl$ (1 mL) and a solution of 3,5-bis-trifluoromethyl-benzyl amine (0.05 g, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1 mL) was added. The resin was shaken for 20 min at room temperature and then $NaBH(OAc)_3$ (0.045 g, 0.2 mmol, 5 eq) was added. The mixture was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (1X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin tested positive with chloranil and negative with 2,4-dinitrophenylhydrazine.

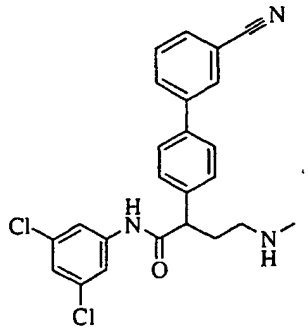
The resin was suspended in pyridine (1 mL) and a solution of 2-(3,4-dichloro-phenyl)-pent-4-enoyl chloride (~0.054 g, 0.2 mmol, 5 eq) in CH_2Cl_2 (1 mL) was added. The resin was shaken at room temperature for 16 h. The solution was filtered and the resin was washed with MeOH (3X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). This procedure was repeated using the same reaction and washing conditions. An aliquot of the resin gave a negative bead test with chloranil. The resin was shaken at room temperature for 14 h with a solution of OsO_4 (4 % in H_2O, 0.052 mL, 0.008 mmol, 0.2 eq) and NMMO (0.05 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) at room temperature for 14 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (2X), pyridine (1X, shake for 30 min), MeOH (2X) and CH_2Cl_2 (3X). A solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in

acetone-H_2O (1:1, 3 mL) was added and the mixture shaken for 2 h. The solution was filtered and the resin was washed with H_2O (2X), acetone (1X). The resin was treated with a fresh solution of $NaIO_4$ (0.085 g, 0.4 mmol, 10 eq) in acetone-H_2O (1:1, 3 mL) and shaken for a further 2 h. The solution was filtered and the resin was washed with H_2O (3X), acetone (1X), MeOH (2X) and CH_2Cl_2 (3X).

The resin was shaken with a solution of N-methylcyclohexylamine 0.026 mL, 0.2 mmol, 5 eq) in $ClCH_2CH_2Cl$ (1.5 mL) for 30 min. $Na(OAc)_3BH$ (0.05 g, 0.2 mmol, 5 eq) was added and the mixture shaken at room temperature for 14 h. The solution was filtered and the resin washed with MeOH (2X), DMF (3X), MeOH (3X) and CH_2Cl_2 (3X). An aliquot of the resin gave a positive chloranil test. The resin was treated with a solution of TFA (25 % in CH_2Cl_2, 3 mL) and shaken for 2 h at room temperature, filtered off and the filtrate was concentrated and purified by Gilson 215 HPLC (10-90% acetonitrile/water) to yield the title compound (0.0039 g, 15%). MS(ESI): 569.1 (M+1), 571.2 (M+3).

EXAMPLE 31

2-(3'-Cyano-biphenyl-4-yl)-N-(3,5-dichloro-phenyl)-4-methylamino-butyramide:



To a solution of 4-bromophenylpent-4-enoyl chloride (1.0 g, 3.7 mmol, EXAMPLE 18) in CH_2Cl_2 (15 mL) was added 3,5-dichloroaniline (0.74 g, 4.5 mmol, 1.2 eq) and Et_3N (1.5 mL, 11.1 mmol, 3 eq). The reaction mixture was stirred at r.t. for 16 h. The mixture was washed with 10% $NaHCO_3$ (10 mL), H_2O (10 mL), 1N HCl (10 mL) and saturated brine, dried (Na_2SO_4), and concentrated. Chromatography on silica gel (10% EtOAc/hexanes) gave 2-(4-bromo-phenyl)-pent-4-enoic acid (3,5-dichloro-phenyl)-amide as a yellow oil (1.5 g, 100%). ^1H NMR

(300 MHz, $CDCl_3$): δ 7.62 (d, 2H), 7.53 (d, 2H), 7.33 (d, 2H), 7.19 (t, 1H), 5.83 (m, 1H), 5.17 (m, 2H), 3.62 (t, 1H), 3.03 (m, 1H), 2.65 (m, 1H).

To an Argon-purged solution of 2-(4-bromo-phenyl)-pent-4-enoic acid (3,5-dichloro-phenyl)-amide (1.5 g, 3.7 mmol) in toluene/EtOH (2:1 v/v, 30 mL) was added 3-cyanophenylboronic acid (0.99 g, 6.7 mmol, 1.8 eq), $Pd(PPh_3)_4$ (160 mg, 0.44 mmol, 12%), and a solution of Na_2CO_3 (2.12 g, 20 mmol, 5.4 eq) in 10 mL of water. The reaction mixture was heated at 90 °C for 16 h. The mixture was partitioned between EtOAc (50 mL) and 10% $NaHCO_3$ (50 mL) and the organic phase separated. The organic phase was washed with 10% $NaHCO_3$ (30 mL) and saturated brine (30 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica gel (20% EtOAc/hexanes) gave 2-(3'-cyano-biphenyl-4-yl)-pent-4-enoic acid (3,5-dichloro-phenyl)-amide as a yellow oil (685 mg, 44%). ^1H NMR (300 MHz, CD_3OD): δ 7.93 (m, 2H), 7.81(m, 2H), 7.66 (m, 4H), 7.49 (m, 2H), 7.12 (t, 1H), 5.89 (m, 1H), 5.21(m, 2H). 3.76 (t, 1H), 3.11(m, 1H), 2.73 (m, 1H).

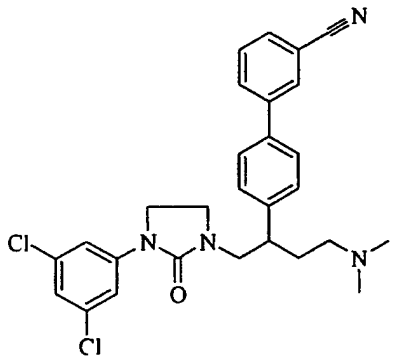
To a solution of 2-(3'-cyano-biphenyl-4-yl)-pent-4-enoic acid (3,5-dichloro-phenyl)-amide (680 mg, 1.6 mmol) in 9 mL of acetone/H_2O (2:1 v/v) was added OsO_4 (4% in H_2O, 100 •L, 1 mmol %) and $NaIO_4$ (860 mg, 4.0 mmol, 2.5 eq). The reaction mixture was stirred at r.t. for 6 h. The mixture was then partitioned between CH_2Cl_2 (20 mL) and 10% $NaHCO_3$ (20 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL x 3) and the combined organic layer was washed with saturated brine (10 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica gel (20% EtOAc/hexanes) gave 2-(3'-cyano-biphenyl-4-yl)-N-(3,5-dichloro-phenyl)-4-oxo-butyramide as a light yellow oil (300 mg, 44%). MS(ESI): 423.0 (M+1).

A mixture of 2-(3'-cyano-biphenyl-4-yl)-N-(3,5-dichloro-phenyl)-4-oxo-butyramide (300 mg, 0.71 mmol) and $MeNH_2$ (2M in THF, 1.77 mL, 3.54 mmol, 5 eq) in 1,2-dichloroethane (3.5 mL) was stirred at r.t. for 1 h and then $Na(AcO)_3BH$ (299 mg, 1.4 mmol, 2 eq) was added. The reaction mixture was stirred at r.t. for 16 h. The mixture was then partitioned between EtOAc (20 mL) and 10% $NaHCO_3$ (10 mL) and the organic phase separated. The organic phase was washed with 10% $NaHCO_3$ (10 mL x 2), saturated brine (10 mL), dried (Na_2SO_4), and concentrated.

Chromatography on silica gel ($Et_3N/MeOH/CH_2Cl_2$ 1:10:90) gave 56.5 mg (18%) of the title compound as a yellowish gum. ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (m, 2H), 7.72 (m, 1H), 7.61 (m, 7H), 7.14 (t, 1H), 4.04 (dd, 1H), 2.85 (t, 2H), 2.59 (s, 3H), 2.50 (m, 1H), 2.16 (m, 1H). MS(ESI): 438.0 (M+1), 440.0 (M+3).

EXAMPLE 32

4'-{1-[3-(3,5-Dichlorophemyl)-2-oxo-imidazolidin-1-ylmethyl]-3-dimethylaminopropyl}-biphenyl-3-carbonitrile:



A solution of 3,5-dichlorophenyl isocyanate (5 g, 26.6 mmol) in *t*-BuOH (100 mL) was heated at 80 °C for 16 h. The mixture was concentrated by rotary evaporation to give a white solid which was triturated with toluene and evaporated to dryness. Addition of toluene and concentration under vacuum gave (3,5-dichlorophenyl)-carbamic acid-*tert*-butyl ester as a white solid (6 g, 22.9 mmol, 84%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 2H), 7.18 (s, 1H), 6.6 (br s, NH), 1.62 (s, 9H).

To a solution of (3,5-dichlorophenyl)-carbamic acid-*tert*-butyl ester (6 g, 22.89 mmol) in DMF (130 mL) at 0 °C under Ar was added NaH (60% dispersion in mineral oil, 1.725 g, 45 mmol, 2 eq). The mixture was stirred at 0 °C for 30 min and then allyl iodide (13.32 mL, 110 mmol, 5 eq) was added over 5 min. The mixture was warmed to room temperature and stirred for 2 h. The mixture was then diluted with EtOAc (200 mL) and washed with saturated aqueous $NaHCO_3$ (200 mL). The aqueous phase was washed with EtOAc (3 x 60 mL) and the combined organic

extracts were washed with saturated aqueous NaCl (200 mL), dried over Na_2SO_4, filtered and concentrated to give a brown oil which was purified by flash column chromatography eluting with 2% EtOAc/hexanes to give allyl-(3,5-dichlorophenyl)-carbamic acid-*tert*-butyl ester as a clear oil (4.632 g, 15.33 mmol, 67%).). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (s, 1H), 7.24 (m, 2H), 6.00 (m, 1H), 5.30 (m, 2H), 4.30 (m, 2H), 1.59 (s, 9H).

A stirred solution of allyl-(3,5-dichlorophenyl)-carbamic acid-*tert*-butyl ester (2.32 g, 7.68 mmol) in CH_2Cl_2 (75 mL) was cooled to –78 °C. Ozone was bubbled through for ~ 5 min (reaction monitored by tlc). Oxygen was then bubbled through for 5 min. Me_2S (5 mL, 77 mmol, 10 eq) was added and the mixture was warmed to room temperature and stirred for 6 h. Following a further addition of Me_2S (5 mL, 77 mmol, 10 eq) the mixture was stirred at room temperature for 14 h. The mixture was concentrated by rotary evaporation and the resulting residue was purified by flash column chromatography eluting with 25% EtOAc/hexanes to yield (3,5-dichlorophenyl)-(2-oxo-ethyl)-carbamic acid-*tert*-butyl ester (1.61 g, 5.3 mmol, 69%) as a pale oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.30 (m, 3H), 4.45 (s, 2H), 1.56 (s, 9H).

To a stirred solution of (3,5-dichlorophenyl)-(2-oxo-ethyl)-carbamic acid-*tert*-butyl ester (0.75 g, 2.46 mmol) in MeOH (15 mL) under Ar at room temperature was added a solution of (R,S) 2-(4-iodophenyl)-pent-4-enylamine (0.741 g, 2.58 mmol, 1.05 eq) in MeOH (5 mL). The mixture was stirred at room temperature for 5 h. $NaBH_4$ (0.140 g, 3.69 mmol, 1.5 eq) was added and the resulting mixture was stirred for a further 1 h, quenched by the addition of NaOH (1 M aqueous solution, 20 mL). The mixture was extracted twice with Et_2O (50 mL total) and the combined organic extracts were washed with saturated aqueous NaCl and dried over Na_2SO_4. Filtration and concentration of the filtrate by rotary evaporation gave the crude product which was purified by flash column chromatography eluting 12% EtOAc/hexanes to give (3,5-Dichloro-phenyl)-{2-[2-(4-iodo-phenyl)-pent-4-enylamino]-ethyl}-carbamic acid tert-butyl ester (0.493 g, 0.85 mmol, 35%) as a pale oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 2H), 7.29 (td, 2H), 7.18 (d, 2H), 7.04

(d, 2H), 5.74 (m, 1H), 5.06 (m, 2H), 3.74 (td, 2H), 2.82 (m, 5H), 2.44 (m, 2H), 1.52 (s, 9H).

To a stirred solution of (3,5-dichloro-phenyl)-{2-[2-(4-iodo-phenyl)-pent-4-enylamino]-ethyl}-carbamic acid tert-butyl ester (0.493 g, 0.85 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added TFA (5 mL). The mixture was stirred and warmed to room temperature for 4 h. The solvent was removed by rotary evaporation and the residue was dissolved in EtOAc and washed twice with $NaHCO_3$ (10% in H_2O). The organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to give N-(3,5-dichloro-phenyl)-N'-[2-(4-iodo-phenyl)-pent-4-enyl]-ethane-1,2-diamine (0.386 g, 0.81 mmol, 95%) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, 2H), 7.03 (d, 2H), 6.56 (t, 1H), 6.50 (d, 2H), 5.75 (m, 1H), 5.08 (m, 2H), 4.42 (br s, NH), 3.15 (m, 2H), 3.40 (m, 5H), 2.44 (m, 2H).

To a stirred solution of N-(3,5-dichloro-phenyl)-N'-[2-(4-iodo-phenyl)-pent-4-enyl]-ethane-1,2-diamine (0.386 g, 0.81 mmol) in toluene (10 mL) was added CDI (0.18 g, 1.1 mmol, 1.4 eq). The mixture was heated to 100 °C for 16 h, then cooled to room temperature, diluted with EtOAc (25 mL) and washed twice with saturated aqueous NaCl (25 mL). The organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to give a dark brown oil. The crude product was purified by flash column chromatography eluting with 10% EtOAc/hexanes to give 1-(3,5-dichloro-phenyl)-3-[2-(4-iodo-phenyl)-pent-4-enyl]-imidazolidin-2-one (0.128 g, 0.255 mmol, 30%) as a pale foam. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 2H), 7.54 (d, 2H), 7.20 (m, 3H), 5.75 (m, 1H), 5.10 (m, 2H), 3.74 (m, 3H), 3.38 (m, 2H), 3.22 (m, 1H), 3.08 (m, 1H), 2.50 (m, 2H).

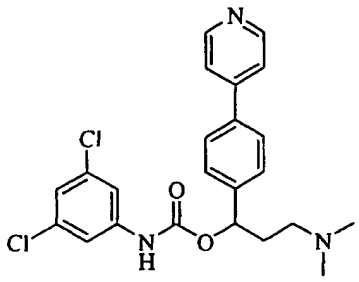
A solution of 1-(3,5-dichloro-phenyl)-3-[2-(4-iodo-phenyl)-pent-4-enyl]-imidazolidin-2-one (0.128 g, 0.255 mmol), 3-cyanophenyl boronic acid (0.113 g, 0.766 mmol, 3 eq), tris(dibenzylideneacetone)dipalladium(0) (0.025g, 0.0255 mmol, 10 mol %), triphenylarsine (0.031g, 0.1 mmol, 40 mol %) and cesium fluoride (0.075g, 0.51 mmol, 2 eq) in DME (13 mL) and ethanol (3 mL) was microwaved at 50W for 7 h and then at 100W for 1 h. The mixture was diluted with EtOAc (50 mL), filtered through a pad of celite 545® and the filtrate washed with saturated aqueous Na_2CO_3 solution (25 mL). The aqueous layer was extracted twice with

EtOAc (50 mL). The combined organic extracts were washed with saturated aqueous Na_2CO_3 solution (25 mL) and saturated aqueous sodium chloride solution (25 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated to give a dark oil. Purification by flash column chromatography eluting 15-20% EtOAc/hexanes gave 4'-{1-[3-(3,5-dichloro-phenyl)-2-oxo-imidazolidin-1-ylmethyl]-but-3-enyl}-biphenyl-3-carbonitrile (0.059 g, 0.125 mmol, 49%) as a dark foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (m, 1H), 7.92 (m, 1H), 7.74 (m, 1H), 7.64 (m, 3H), 7.58 (d, 2H), 7.45 (d, 2H), 7.11 (dd, 1H), 5.80 (m, 1H), 5.12 (m, 2H), 3.75 (m, 3H), 3.55 (m, 1H), 4.42 (m, 1H), 3.26 (m, 2H), 2.58 (dd, 2H).

Ozone was bubbled through a solution of 4'-{1-[3-(3,5-dichloro-phenyl)-2-oxo-imidazolidin-1-ylmethyl]-but-3-enyl}-biphenyl-3-carbonitrile (0.059g, 0.124 mmol) in CH_2Cl_2 (15 mL) at –78 °C. After 5 min, oxygen was bubbled through followed by the addition of DMS (0.1 mL, 12.5 mmol, 10 eq). The mixture was warmed to room temperature and stirred for 18 h. The solvent was removed by rotary evaporation and the resulting residue was dissolved in $ClCH_2CH_2Cl$ (2 mL) and dimethylamine (2M in THF, 0.06 mL, 0.12 mmol, 1 eq) was added. The mixture was stirred at room temperature for 1 h and then $Na(OAc)_3BH$ (0.033g, 0.16 mmol, 1.3 eq) was added. The mixture was stirred at room temperature for 16 h and then partitioned between saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (20 mL). The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated to yield the crude product. Purification by HPLC gave the title compound 4'-{1-[3-(3,5-dichlorophemyl)-2-oxo-imidazolidin-1-ylmethyl]-3-dimethylaminopropyl}-biphenyl-3-carbonitrile (0.016g, 0.02 mmol, 16%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (m, 1H), 7.92 (dt, 1H), 7.76 (dt, 1H), 7.68 (m, 3H), 7.56 (d, 2H), 7.46 (d, 2H), 7.14 (t, 1H), 3.82 (m, 3H), 3.44 (m, 3H), 3.4 (m, 2H), 2.94 (br s, 6H), 2.30 (m, 2H); MS(ESI): 507.1 (M+1), 509.0 (M+3).

EXAMPLE 33

(3,5-Dichloro-phenyl)-carbamic acid 3-dimethylamino-1-(4-pyridin-4-yl-phenyl)-propyl ester:



A mixture of 2-(4-iodo-phenyl)-pent-4-enenitrile (2.8 g, 9.9 mmol, intermediate for preparing EXAMPLE 2), OsO_4 (0.7 mL, 4% in water, 0.10 mmol), and $NaIO_4$ (4.44 g, 20.8 mmol) in 2:1 acetone/H_2O (100 mL) was stirred at room temperature for 16 h. TLC (1:1 hexanes/EtOAc) showed no starting material left. The mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (50 mL x 4). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated by rotary evaporation. Purification by silica gel chromatography (1:1 hexanes/EtOAc) gave 2-(4-iodo-phenyl)-4-oxo-butyronitrile as a yellowish oil, 1.9 g (68%). ^1H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.84 (d, 2H), 7.24 (d, 2H), 4.44 (t, 1H), 3.33 (dd, 1H), 3.14 (dd, 1H).

To a solution of 2-(4-iodo-phenyl)-4-oxo-butyronitrile (2.03 g, 7.1 mmol) in $ClCH_2CH_2Cl$ (50 mL) was added dimethylamine (14.3 mL, 2M in THF, 28.6 mmol, 4 eq) and the mixture was left stirring at room temperature for 1 h. $Na(OAc)_3BH$ (6.04 g, 28.6 mmol, 4 eq) was added and the mixture was stirred at room temperature for 16 h. The reaction was quenched by adding aqueous saturated $NaHCO_3$ (50 mL) and the mixture was extracted with EtOAc (50 mL x 3). The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (50% EtOAc/hexanes) to give 4-dimethylamino-2-(4-iodo-phenyl)-butyronitrile as a dark brown solid, 2.09 g (94%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 2H), 7.22 (d, 2H), 4.10 (t, 1H), 2.56 (m, 1H), 2.41 (m, 1H), 2.34 (s, 6H), 2.20 (m, 1H), 2.05 (m, 1H).

To a solution of 4-dimethylamino-2-(4-iodo-phenyl)-butyronitrile (1.02 g, 3.2 mmol) in 2:1 toluene/EtOH (30 mL) was added 2M Na_2CO_3 (10 mL, 20 mmol), pyridine-4-boronic acid pinacol cyclic ester (1.0 g, 4.9 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.31 mmol). The resulting mixture was heated at 90 °C under Ar for 16 h. TLC

(10% MeOH/CH_2Cl_2) showed no starting material left. The mixture was diluted with EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ (50 mL x 3), saturated aqueous NaCl (50 mL x 3), dried over Na_2SO_4 and concentrated by rotary evaporation. The crude residue was purified using silica gel chromatography (2-10% MeOH/CH_2Cl_2 gradient) to give 4-dimethylamino-2-(4-pyridin-4-yl-phenyl)-butyronitrile as a brown oil, 680 mg (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.79 (dd, 2H), 7.78 (d, 2H), 7.60 (m, 4H), 4.22 (dd, 1H), 2.61 (m, 1H), 2.46 (m, 1H), 2.37 (s, 6H), 2.24 (m, 1H), 2.15 (m, 1H).

To a solution of 4-dimethylamino-2-(4-pyridin-4-yl-phenyl)-butyronitrile (680 mg, 2.56 mmol) in THF (5 mL) was added $LiAlH_4$ (1M in THF, 26 mL, 26 mmol) and the mixture was stirred at room temperature for 16 h. TLC (10% MeOH/CH_2Cl_2) showed no starting material left and a new low Rf spot was formed. The mixture was treated with 1.74 mL of H_2O, followed by 3.48 mL of 1N aqueous NaOH, and then 5.2 mL of H_2O. After 30 min of stirring, the mixture was filtered and the filtrate was dried over Na_2SO_4 and concentrated to give 3-dimethylamino-1-(4-pyridin-4-yl-phenyl)-propan-1-ol as a yellowish solid, 300 mg (46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (dd, 2H), 7.74 (m, 2H), 7.62 (m, 4H), 5.12 (dd, 1H), 2.82 (m, 1H), 2.64 (m, 1H), 2.44 (s, 6H), 1.97 (m, 2H).

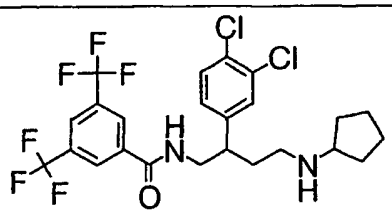
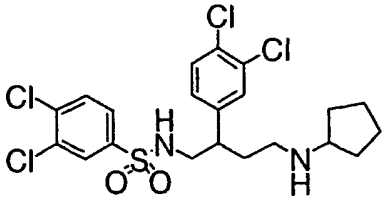
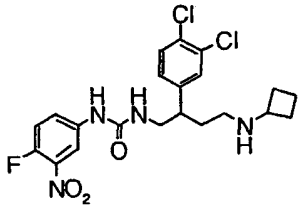
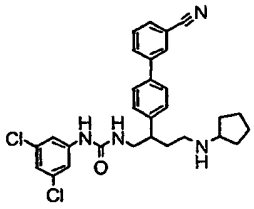
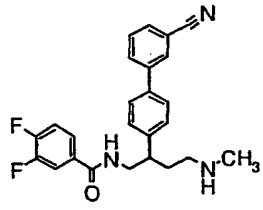
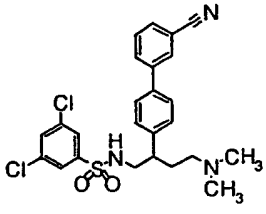
To a solution of 3-dimethylamino-1-(4-pyridin-4-yl-phenyl)-propan-1-ol (100 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) was added 3,5-dichlorophenylisocyanate (70 mg, 0.37 mmol) and the mixture was stirred at room temperature for 16 h. The mixture was concentrated to give a light brown oil, which was then purified by silica gel chromatography (5-10% MeOH/DCM gradient) to afford the title compound (3,5-dichloro-phenyl)-carbamic acid 3-dimethylamino-1-(4-pyridin-4-yl-phenyl)-propyl ester as a white solid, 131 mg (91%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.77 (dd, 2H), 7.72 (d, 2H), 7.58 (m, 3H), 7.48 (d, 2H), 7.12 (t, 1H), 5.94 (t, 1H), 2.49 (m, 2H). 2.36 (s, 6H), 2.33 (m, 1H), 2.21 (m, 1H); MS(ESI): 444.1 (M+1), 446.1 (M+3).

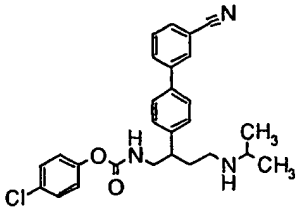
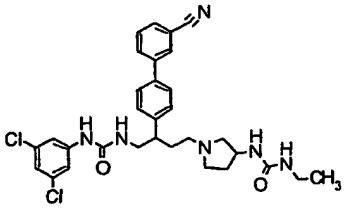
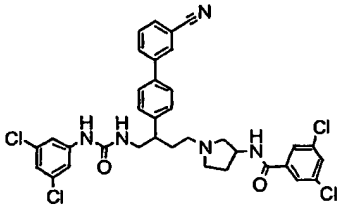
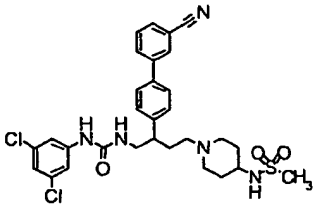
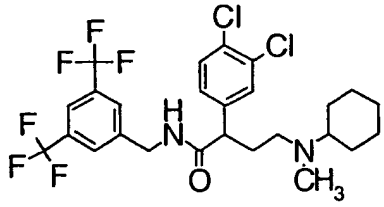
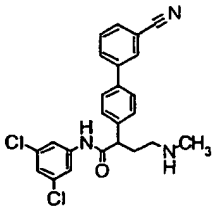
Table I provides additional Examples (#34-457) of MCH active compounds that were prepared using the methods as described for Examples 20-33.

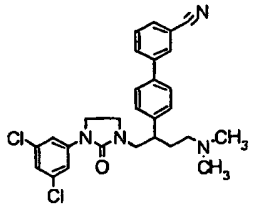
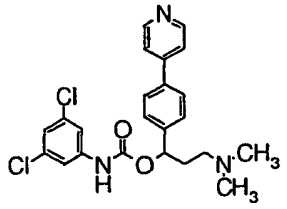
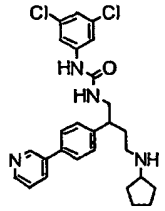
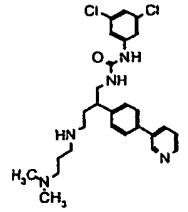
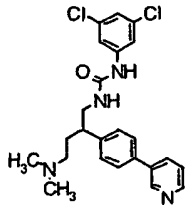
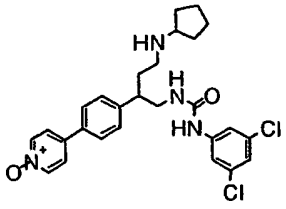
MCH Assay PCOP Protocol:

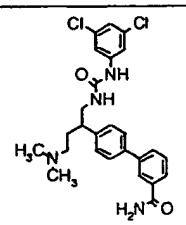
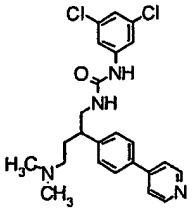
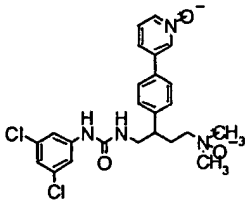
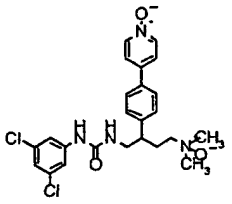
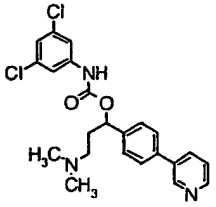
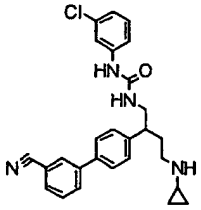
A reaction mixture of 10 µg hMCHR-CHO overexpressing membranes (from Receptor Biology, Inc., Beltsville, Maryland, or internally produced) and 100 µg/well WGA-SPA beads (from Amersham Pharmacia Biotech, Inc., Piscataway, New Jersey)/ 100 µl was prepared in MCHR assay buffer (25 mM HEPES, pH 7.4, 10 mM NaCl, 10 mM $MgCl_2$, 5 mM $MnCl_2$, 0.1%BSA). A 2.0 nM stock of ligand, [^{125}I]-MCH (from Perkin Elmer Life Sciences, Inc., Boston, Massachusetts) was prepared in the MCHR assay buffer. 40X stock solutions of test compounds were prepared in DMSO and then added to a 96-well assay plate (Corning #3604, Corning, New York) as follows: 5 µl test compound, test compound or DMSO, 45 µl MCHR assay buffer, 100 µl of reaction mixture, 50 µl of ligand stock (Final [Ligand] = 0.5 nM). The assay plates were shaken for 5 minutes on a plate shaker, then incubated for 2 hours before cpm/well were determined in a Microbeta Trilux counter (from PerkinElmer Wallac, Inc., Gaithersburg, Maryland). Percent inhibition of total binding-non-specific binding (2.5 µM MCH) was determined for IC_{50} values.

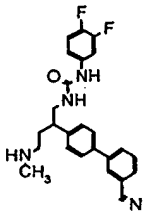
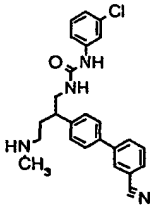
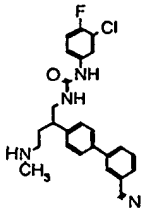
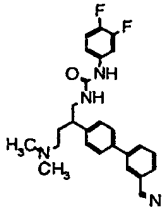
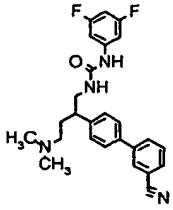
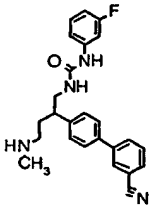
Table I. MCH Antagonist Compounds- A: Ki= 0.4-50 nM; B: Ki = 51-500 nM; C: Ki = 501-2,500 nM

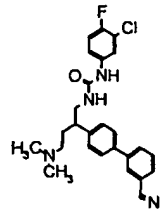
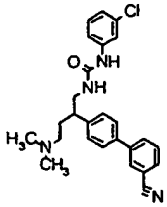
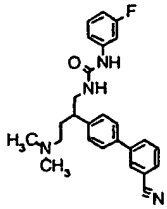
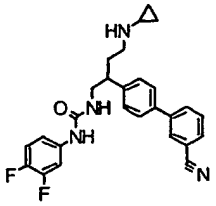
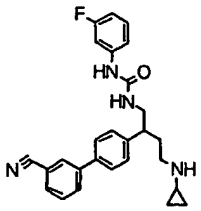
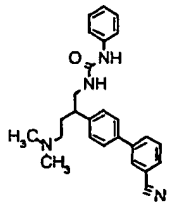
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
20		540.1169	541.1, 543.1	C
21		508.0312	509.1, 511.0, 513.0	C
22		468.1131	469.0, 471.0	C
23		520.1796	521.0, 523.0	C
24		419.1809	420.1, 421.1	C
25		501.1044	502.1, 504.1	C

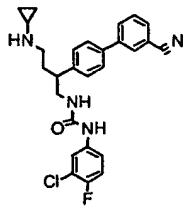
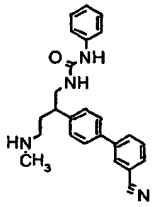
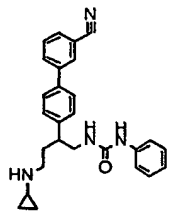
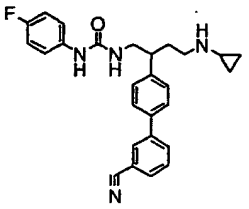
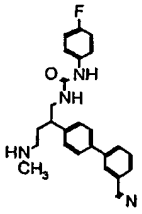
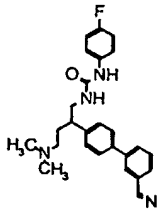
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
26		461.1870	462.2	C
27		592.2120	593.1, 595.1	C
28		693.1231	693.9, 695.9, 697.9	C
29		613.1681	614.1, 616.1	C
30		568.1482	569.1, 571.2	C
31		437.1061	438.0, 440.0	C

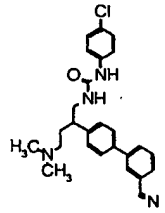
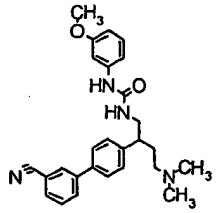
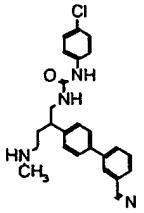
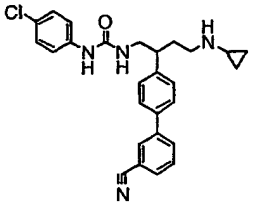
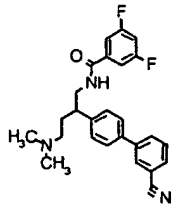
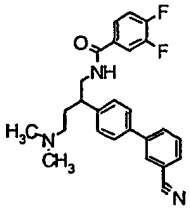
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
32		506.1640	507.1, 509.0	C
33		443.1167	444.1, 446.1	C
34		496.1796	497.1, 499.1	A
35		513.2062	514.1, 516.0	A
36		456.1483	457.2, 459.2	A
37		512.1745	513.2, 515.3	A

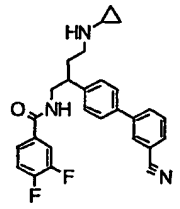
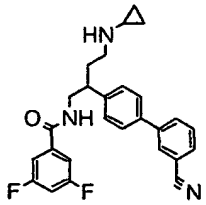
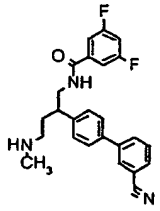
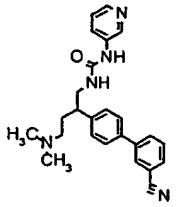
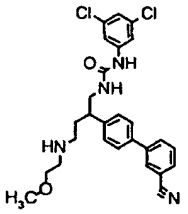
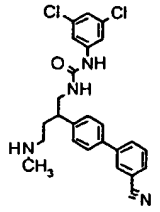
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
38		498.1589	499.2, 501.1	A
39		456.1483	457.2, 459.2	B
40		488.1382	489.1, 491.1	C
41		488.1382	489.1, 491.1	C
42		443.1167	444.1, 446.1	C
43		458.1873	459.0, 461.1	A

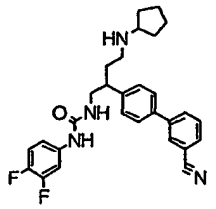
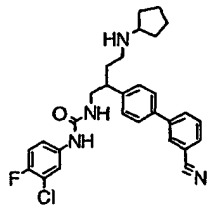
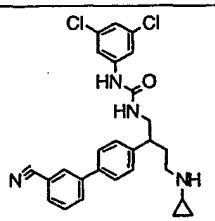
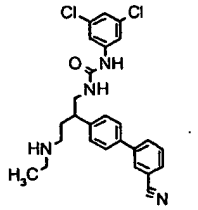
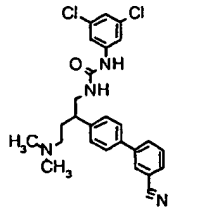
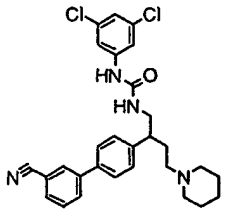
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
44		434.1918	435.0, 436.1	A
45		432.1717	432.9, 435.0	A
46		450.1622	451.0, 453.0	A
47		448.2074	449.1, 450.2	A
48		448.2074	449.1, 450.0	A
49		416.2012	417.0, 418.1	A

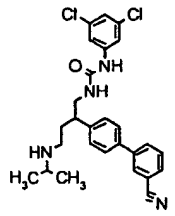
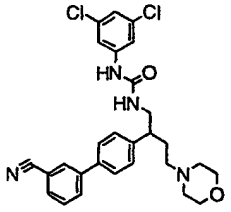
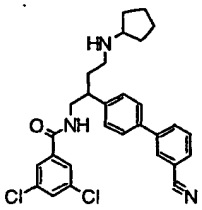
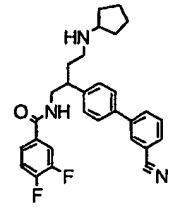
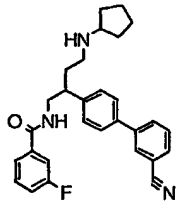
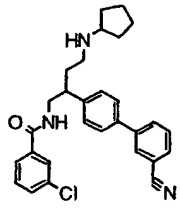
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
50		464.1779	465.0	A
51		446.1873	447.1, 449.1	A
52		430.2169	431.1, 432.1	A
53		460.2074	461.0, 462.1	A
54		442.2169	443.1	A
55		412.2263	413.1, 414.1	A

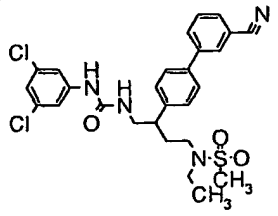
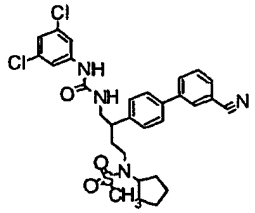
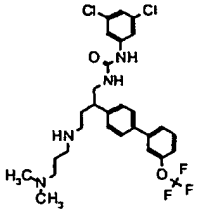
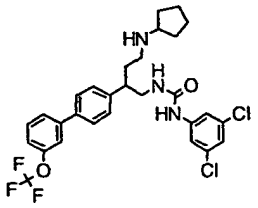
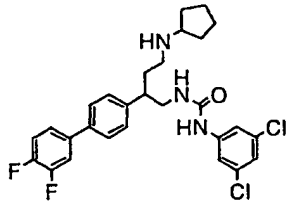
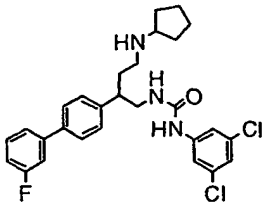
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
56		476.1779	477.0, 479.1	A
57		398.2106	399.0, 400.0	A
58		424.2263	425.0, 426.2	A
59		442.2169	443.0, 444.1	A
60		416.2012	417.0, 418.1	A
61		430.2169	431.1, 432.1	A

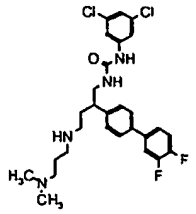
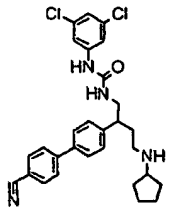
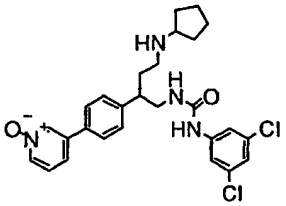
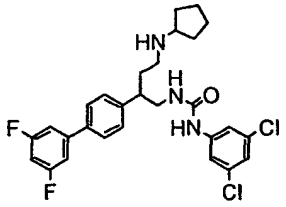
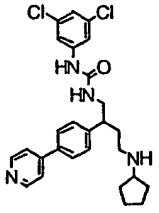
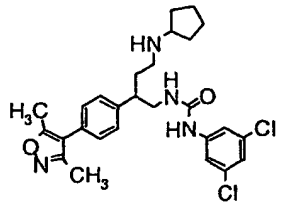
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
62		446.1873	447.1, 449.1	A
63		442.2369	443.1	A
64		432.1717	433.0, 434.0	A
65		458.1873	459.1, 461.0	A
66		433.1965	434.1, 335.2	A
67		433.1965	434.1, 435.1	B

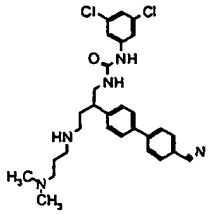
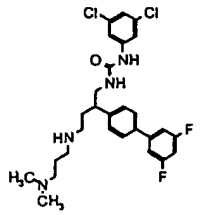
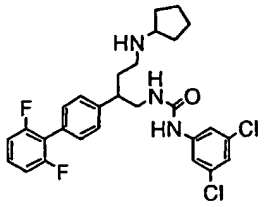
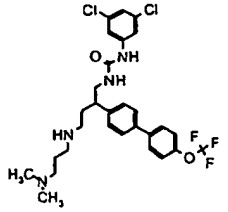
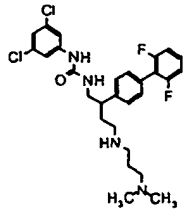
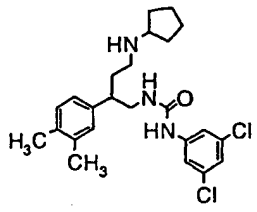
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
68		445.1965	446.1, 447.1	B
69		445.1965	446.1, 447.1	B
70		419.1809	420.1, 421.1	B
71		413.2215	414.0	B
72		510.1589	511.1, 513.0	A
73		466.1327	467.4, 469.1	A

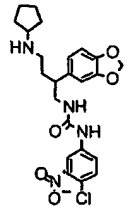
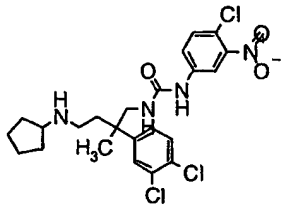
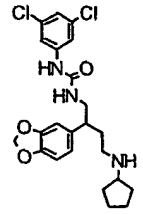
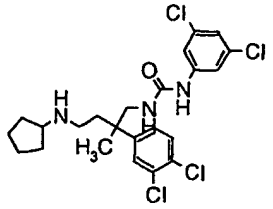
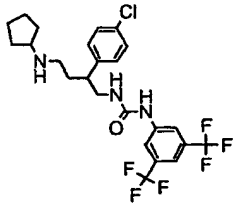
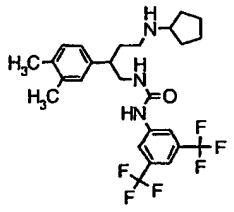
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
74		488.2387	489.1, 490.1	A
75		504.2092	505.1, 507.1	A
76		492.1483	493.0, 494.0, 495.0, 496.0	A
77		480.1483	481.0, 483.0	A
78		480.1483	481.1, 483.1	A
79		520.1796	521.1, 523.1	A

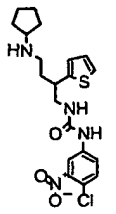
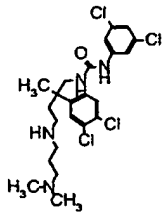
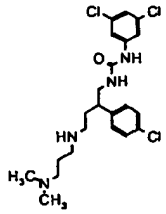
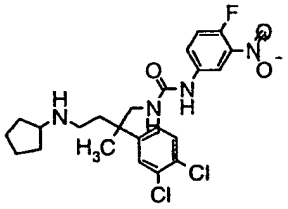
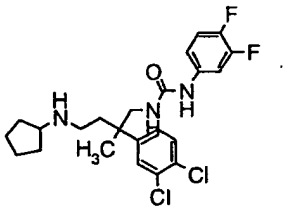
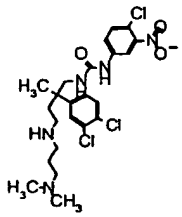
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
80		494.1640	495.0, 497.1	A
81		522.1589	523.1, 525.1	A
82		505.1687	506.1, 508.1	B
83		473.2278	474.1, 475.2	B
84		455.2373	456.1, 457.2	B
85		471.2077	472.1, 473.1	B

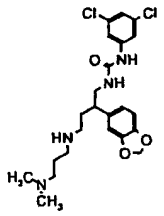
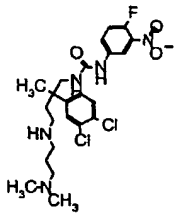
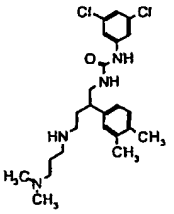
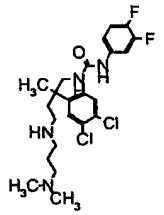
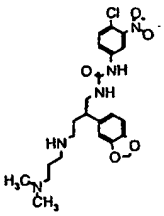
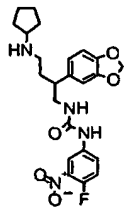
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
86		558.1259	558.9, 560.8	B
87		598.1572	598.9, 601.0	C
88		596.1932	597.1, 599.0	A
89		579.1667	579.9, 582.1	A
90		531.1655	532.0, 534.1	A
91		513.1750	514.1, 516.0	A

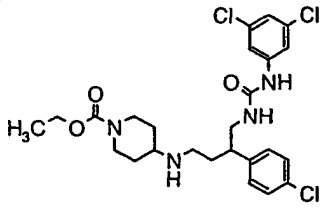
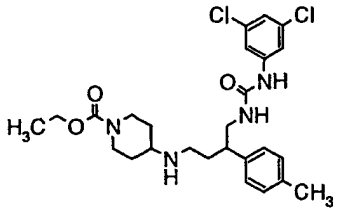
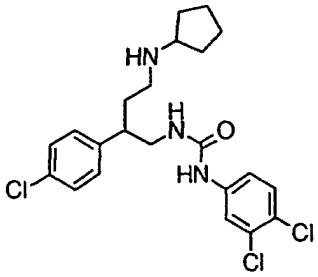
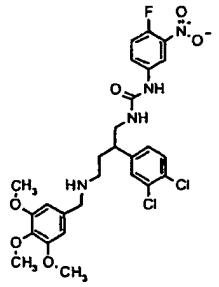
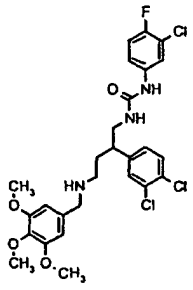
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
92		548.1921	549.0, 551.1	A
93		520.1796	521.0, 523.1	A
94		512.1745	513.0, 515.1	A
95		531.1655	532.0, 534.1	A
96		496.1796	497.3, 499.3	B
97		514.1902	515.0, 517.3	B

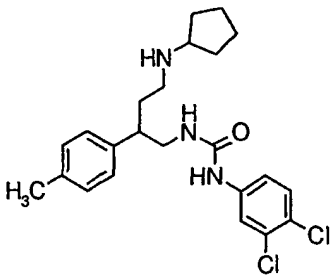
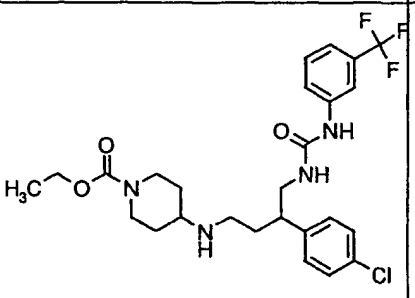
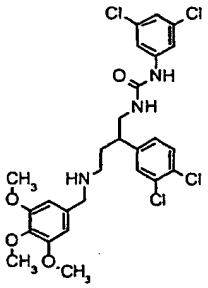
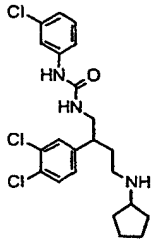
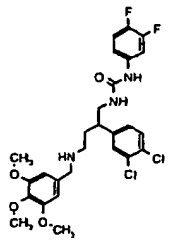
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
98		537.2062	538.1, 540.1	B
99		548.1921	549.0, 551.1	B
100		531.1655	532.0, 534.0	B
101		596.1932	597.0, 599.2	B
102		548.1921	549.0, 551.1	C
103		447.1844	448.1, 450.1	B

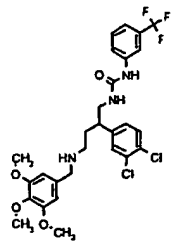
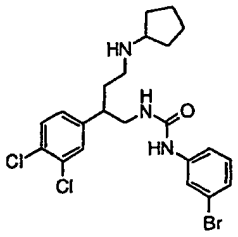
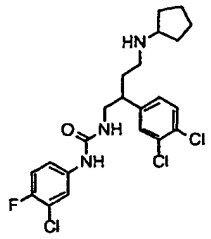
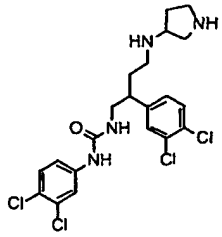
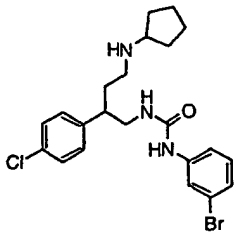
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
104		474.1670	475.1, 477.0	B
105		512.1148	513.0, 515.1, 517.1	B
106		463.1429	464.1, 466.0	B
107		501.0908	502.0, 503.9, 505.1	B
108		521.1668	522.1, 523.0	B
109		515.2371	516.1	B

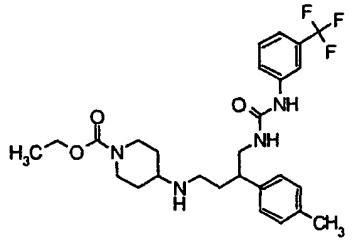
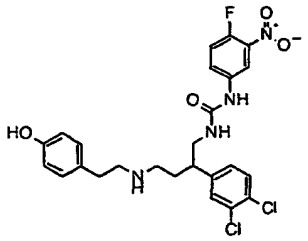
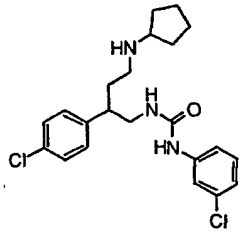
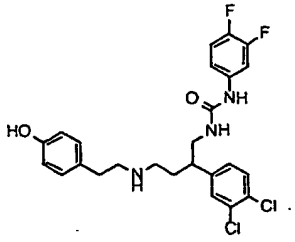
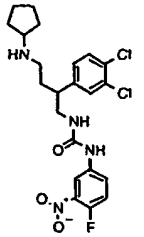
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
110		436.1336	437.0, 439.0	B
111		518.1173	518.9, 520.9, 523.0	B
112		470.1407	470.9, 472.9	C
113		496.1444	497.0, 499.0	C
114		469.1499	470.0, 472.1	C
115		529.1414	530.0, 532.1	C

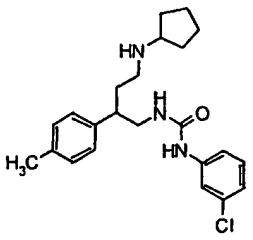
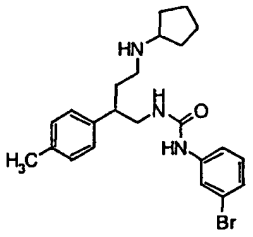
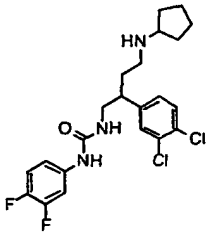
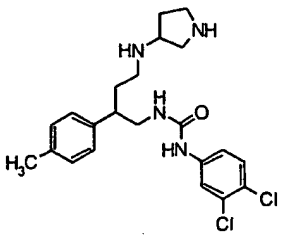
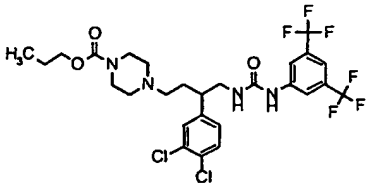
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
116		480.1695	481.0, 483.0	C
117		513.1709	514.0, 516.0	C
118		464.2109	465.1, 467.0	C
119		486.1764	487.1, 489.0	C
120		491.1935	492.1	C
121		458.1965	459.1	C

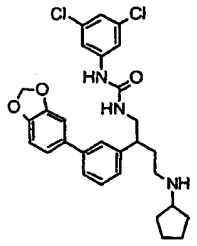
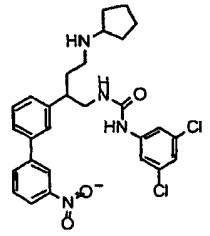
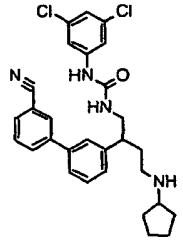
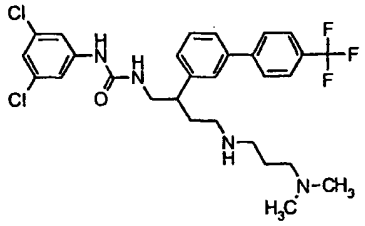
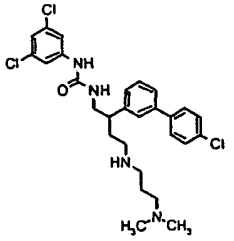
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
122		540.1461	541.0, 543.0, 545.1	B
123		520.2008	521.1, 523.0	B
124		453.1141	454.0, 456.0	B
125		594.1448	594.8, 596.8, 597.9	B
126		583.1207	583.8, 585.8, 587.1	B

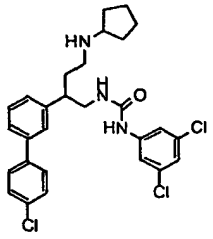
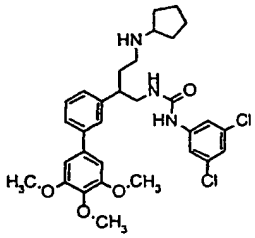
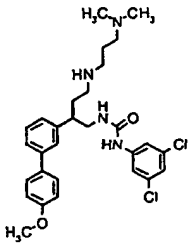
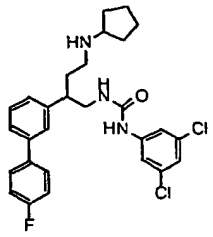
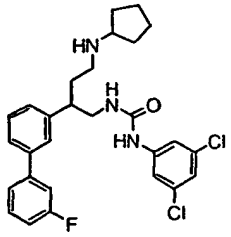
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
127		433.1687	434.1, 436.1, 438.0	B
128		540.2115	541.0, 543.1, 544.1	B
129		599.0912	599.8, 601.8, 603.8	B
130		453.1141	454.0, 455.9, 458.0	B
131		567.1503	567.8, 569.9, 570.9	B

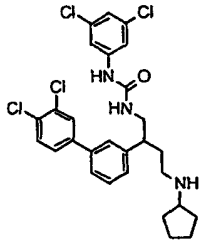
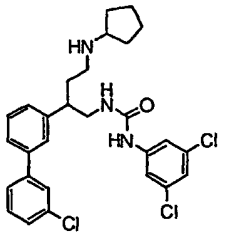
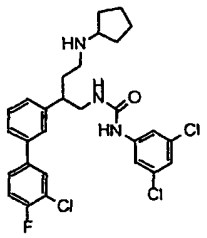
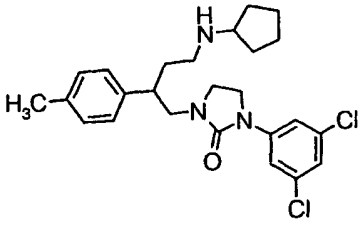
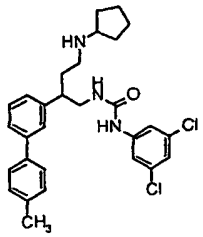
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
132		599.1565	599.8, 601.9, 602.9	B
133		497.0636	497.9, 499.9, 502.0	B
134		471.1047	472.0, 475.0, 476.0	B
135		488.0704	488.9, 490.9, 493.0	B
136		463.1025	464.0, 466.0, 468.1	B

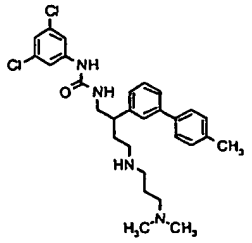
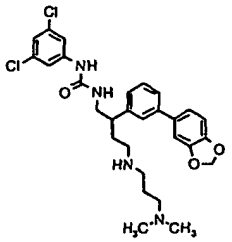
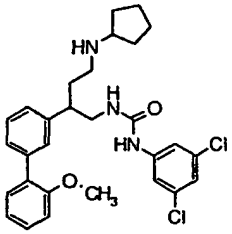
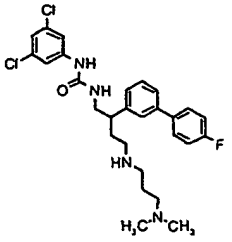
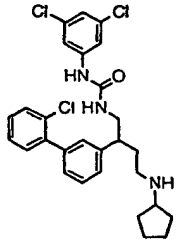
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
137		520.2661	521.1, 522.2	B
138		534.1236	535.0, 537.0	B
139		419.1531	420.0, 421.9, 423.1	C
140		507.1292	508.0, 510.0, 511.1	C
141		482.1287	483.0, 485.0	C

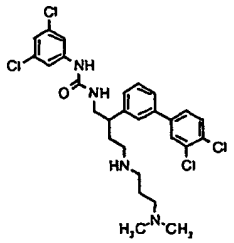
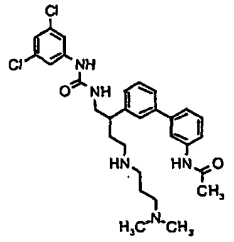
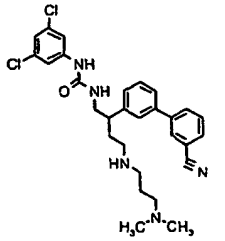
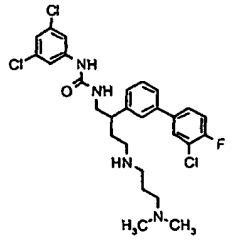
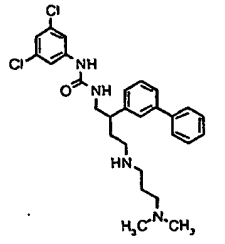
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
142		399.2077	400.0, 402.1	C
143		443.1572	444.1, 447.0	C
144		455.1342	456.0, 458.0	C
145		434.1640	435.0, 437.0	C
146		642.1599	643.0	B

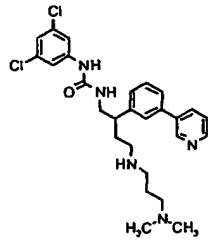
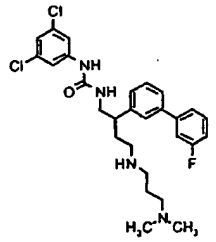
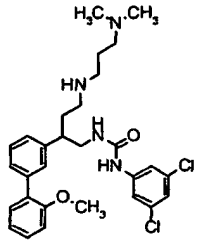
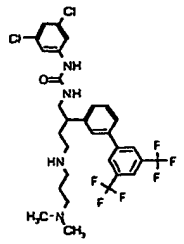
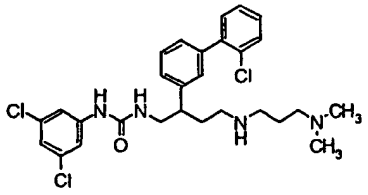
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
147		539.1742	540.1, 542.0	B
148		540.1695	541.0, 543.2	B
149		520.1796	521.0, 523.1	B
150		580.1983	581.1, 583.0	B
151		546.1720	547.0, 549.0	B

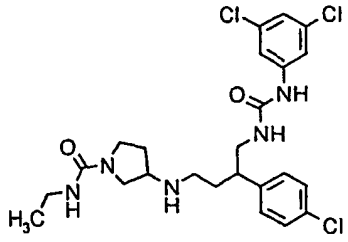
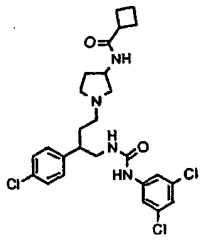
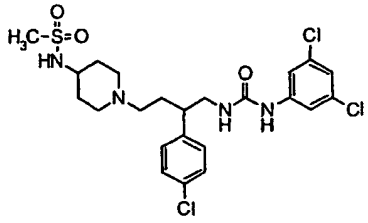
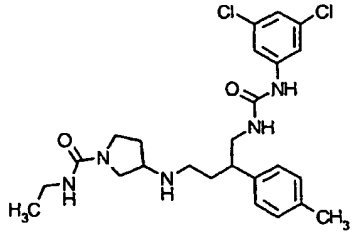
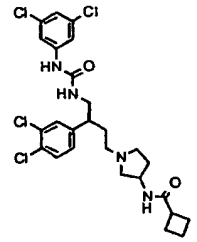
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
152		529.1454	530.0, 532.0	B
153		585.2161	586.0, 588.0	B
154		542.2215	543.1, 545.1	B
155		513.1750	514.1, 516.0	B
156		513.1750	514.0, 516.1	B

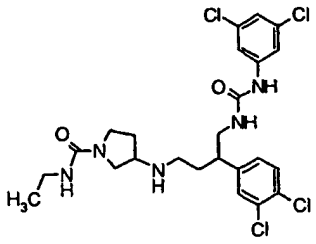
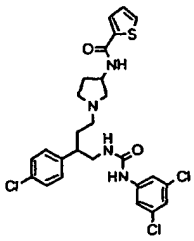
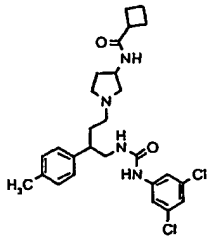
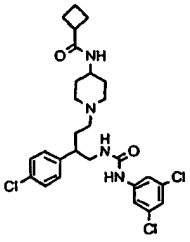
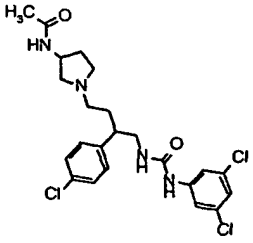
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
157		563.1064	564.1, 566.0, 568.0	B
158		529.1454	530.0, 532.0	B
159		547.1360	548.0, 550.1	B
160		459.1844	460.1, 462.2	B
161		509.2000	510.0, 512.1, 514.1	C

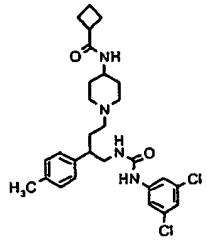
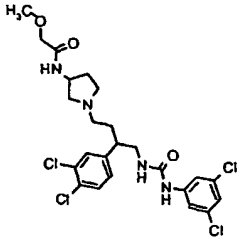
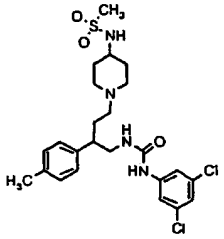
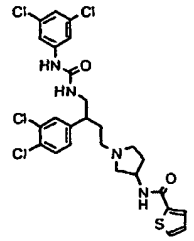
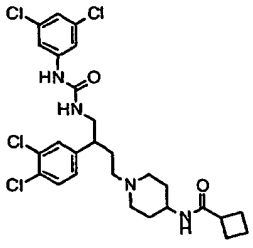
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
162		526.2266	527.0, 529.1	C
163		556.2008	557.1, 559.1	C
164		525.1950	526.1, 528.1	C
165		530.2015	531.0, 533.1	C
166		529.1454	530.0, 532.0	C

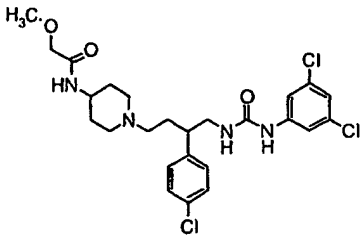
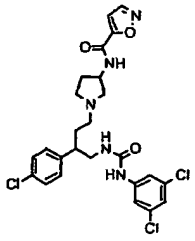
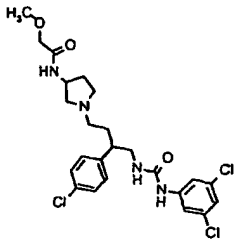
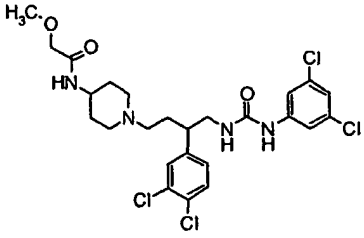
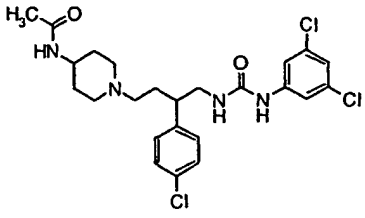
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
167		580.1330	581.0, 582.9, 585.0	C
168		569.2324	570.1, 572.2	C
169		537.2062	538.1, 540.1	C
170		564.1625	565.0, 567.0	C
171		512.2109	513.1, 515.0	C

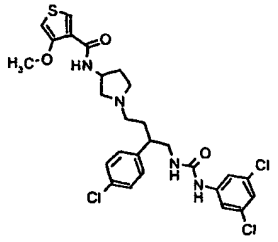
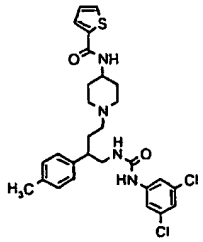
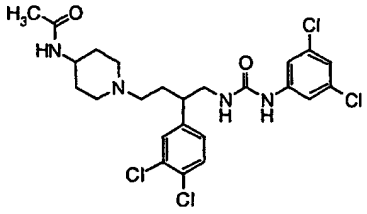
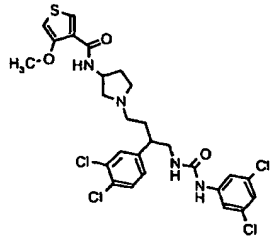
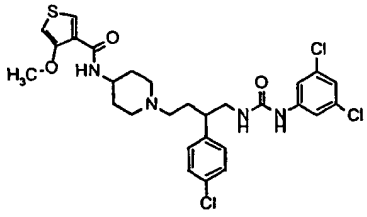
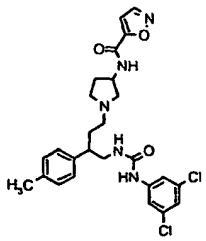
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
172		513.2062	514.0, 516.2	C
173		530.2015	531.1, 533.1	C
174		542.2215	543.1, 545.1	C
175		648.1857	649.0, 651.0	C
176		546.1720	547.0, 549.0	C

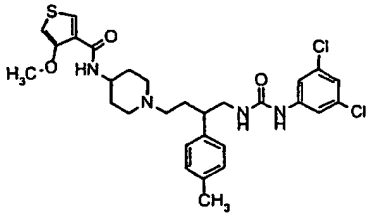
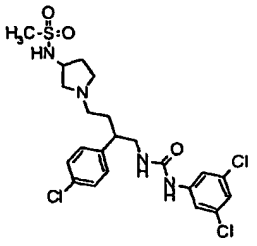
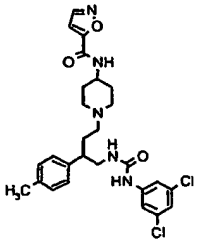
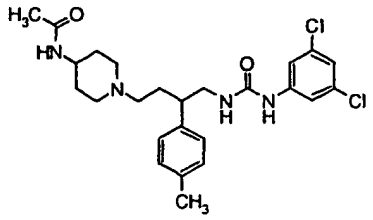
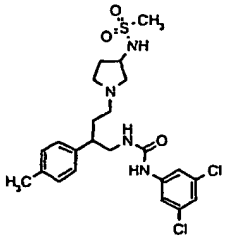
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
177		525.1465	525.9, 527.9, 530.0	B
178		536.1512	537.1, 539.1, 541.2	B
179		546.1026	547.1, 551.1	B
180		505.2011	506.0, 508.1	B
181		570.1122	571.0, 573.0, 575.1	B

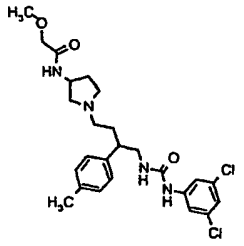
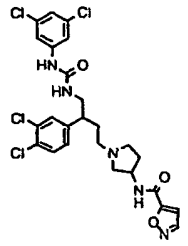
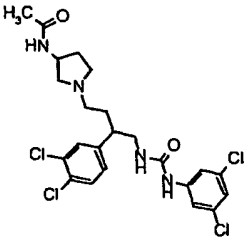
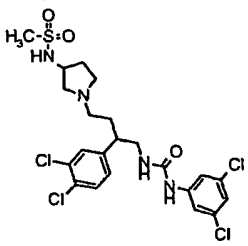
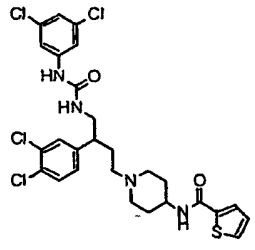
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
182		559.1075	559.9, 562.0, 563.9	B
183		564.0920	565.0, 567.0, 569.1	B
184		516.2058	517.1, 519.3	B
185		550.1669	551.0, 553.1	B
186		496.1199	497.1, 501.1	B

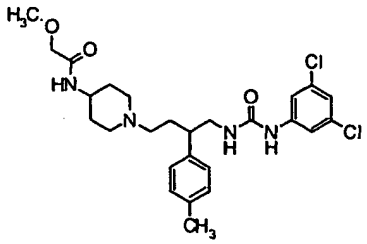
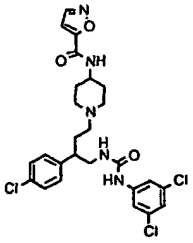
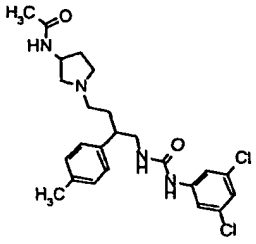
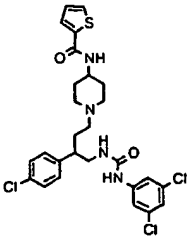
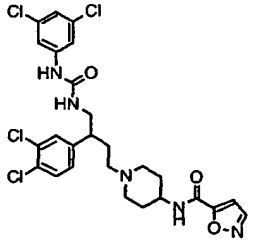
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
187		530.2215	531.1, 533.2	B
188		560.0915	561.0, 563.0, 565.1	B
189		526.1572	527.0, 529.1	B
190		598.0530	598.9, 601.0, 603.0	B
191		584.1279	585.2, 587.1, 589.1	B

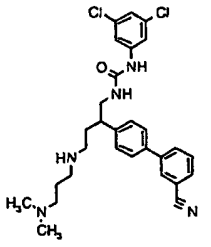
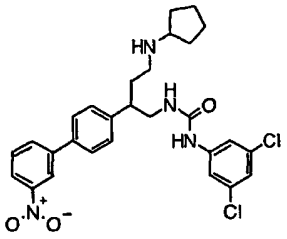
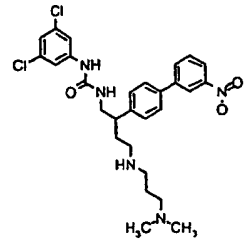
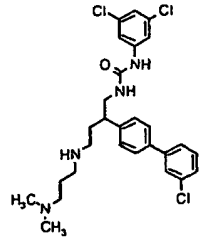
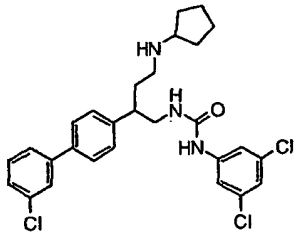
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
192		540.1461	541.0, 543.0	B
193		549.1101	552.0, 554.1	B
194		526.1305	527.1, 529.0	B
195		574.1072	575.1, 577.0, 579.1	B
196		510.1356	511.0, 513.1	B

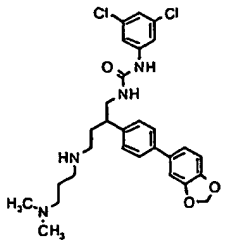
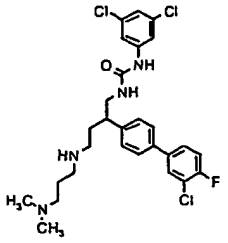
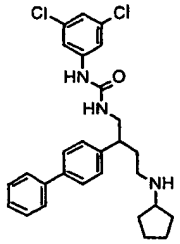
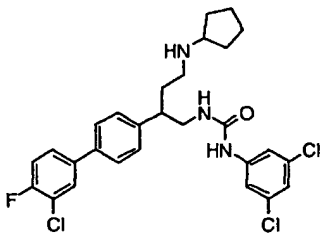
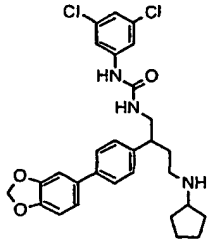
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
197		594.1026	597.0, 599.1	B
198		558.1623	559.1, 561.2	B
199		544.0966	545.0, 547.0, 549.0	B
200		628.0636	629.0, 631.0, 632.9	C
201		608.1182	609.1, 611.0	C
202		529.1647	530.1, 532.1	C

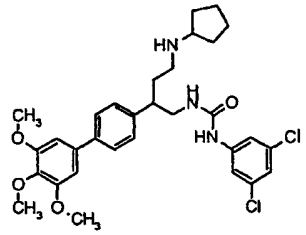
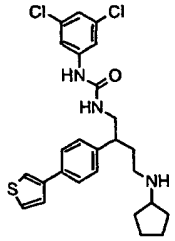
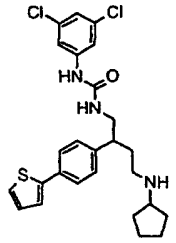
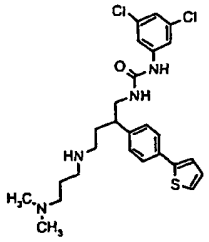
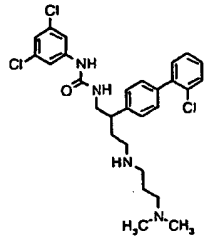
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
203		588.1728	589.0, 591.1	C
204		532.0869	533.0, 535.0	C
205		543.1804	544.1, 546.2	C
206		490.1902	491.1, 493.2	C
207		512.1415	513.0, 515.0	C

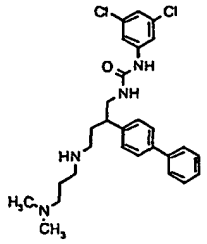
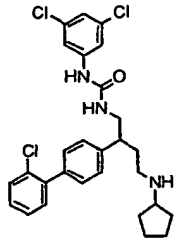
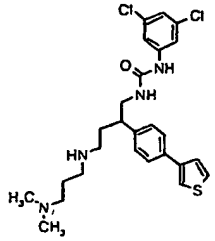
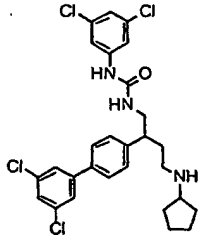
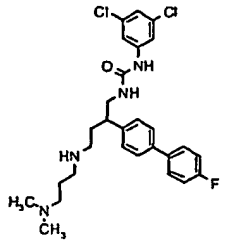
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
208		506.1851	507.1, 509.1	C
209		583.0711	584.0, 586.0, 588.0	C
210		530.0809	531.0, 533.0, 535.0	C
211		566.0479	567.0, 569.0, 571.0	C
212		612.0687	613.2, 615.0	C

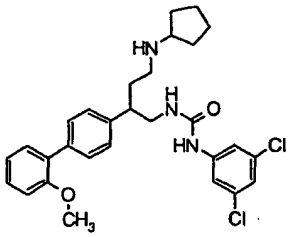
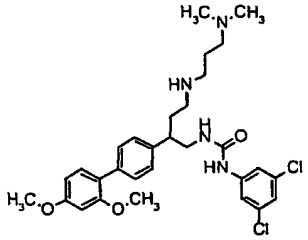
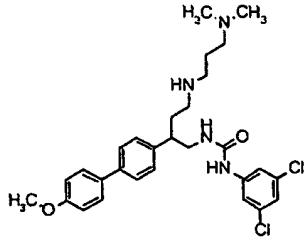
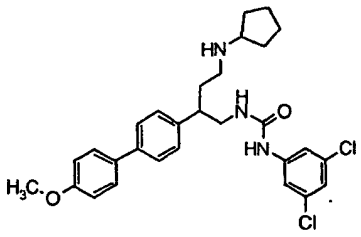
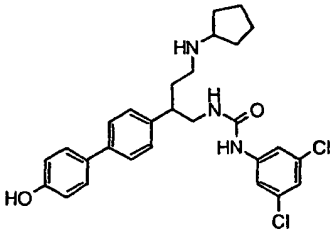
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
213		520.2008	521.1, 523.1	C
214		563.1257	564.0, 566.1, 568.0	C
215		476.1745	477.1, 479.1	C
216		578.1076	579.1, 581.0	C
217		597.0868	598.0, 600.1, 602.2	C

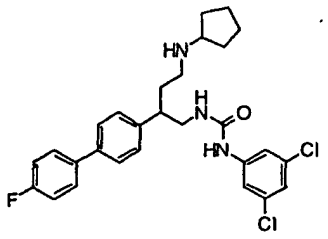
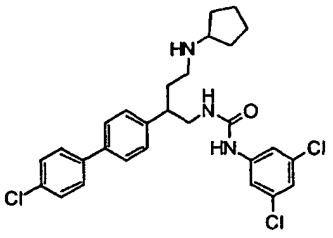
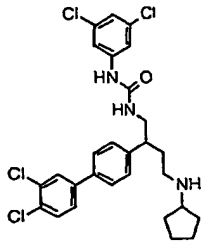
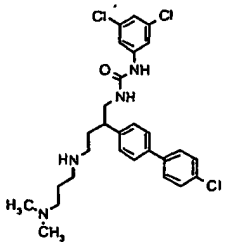
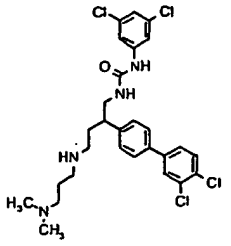
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
218		537.2062	538.0, 548.1	A
219		540.1695	541.1, 543.0	A
220		557.1960	558.0, 568.1	A
221		546.1720	547.0, 549.0	A
222		529.1454	530.0, 532.1	A

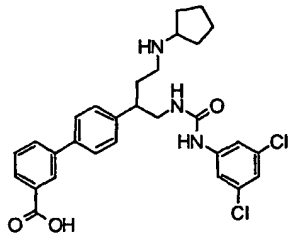
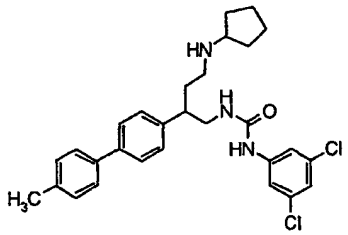
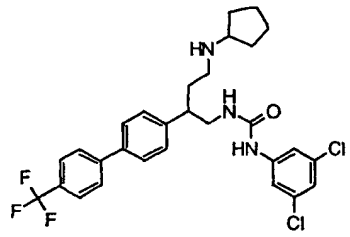
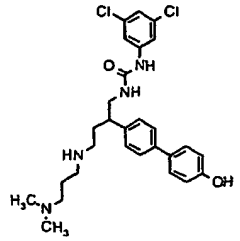
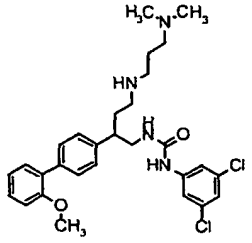
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
223		556.2008	557.0. 559.0	A
224		564.1625	565.0. 567.0. 569.1	A
225		495.1844	496.1, 498.1	A
226		547.1360	548.1. 550.0. 552.0	B
227		539.1742	540.0, 542.0	B

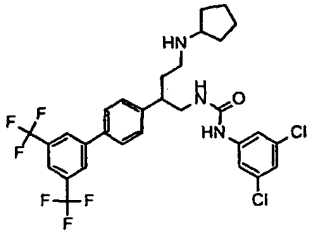
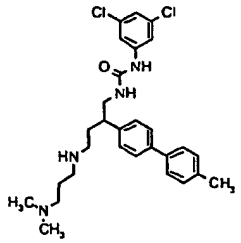
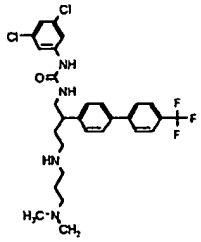
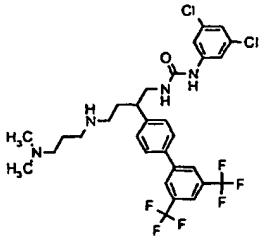
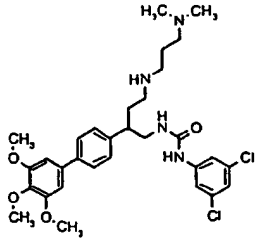
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
228		585.2161	586.2, 588.1	B
229		501.1408	502.1, 504.0	B
230		501.1408	502.1, 504.0	B
231		518.1674	519.0, 521.0	B
232		546.1720	547.1, 549.0, 551.0	B

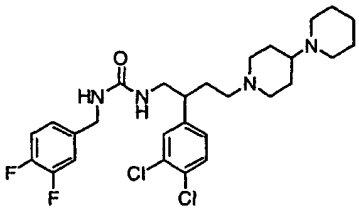
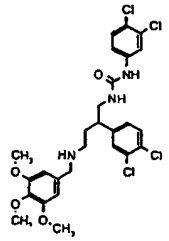
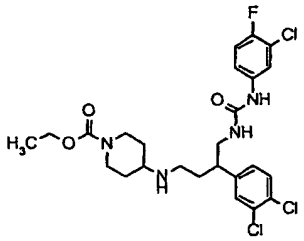
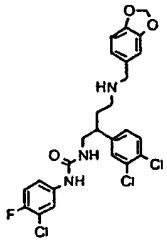
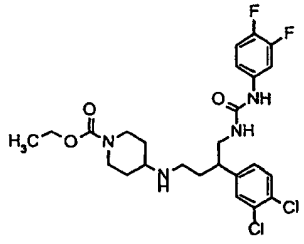
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
233		512.2109	513.1, 515.1	B
234		529.1454	530.0, 532.1	B
235		518.1674	519.1, 521.0	B
236		563.1064	564.0, 565.9, 568.0	B
237		530.2015	531.0, 533.0	B

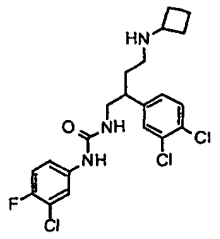
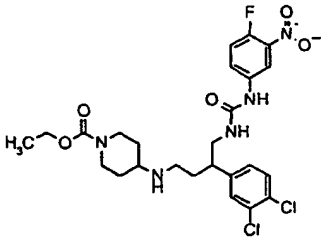
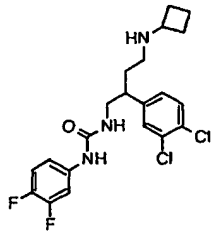
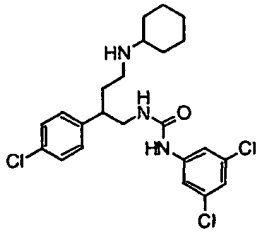
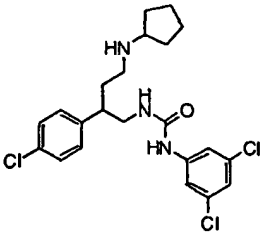
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
238		525.1950	526.1, 528.1	B
239		572.2321	573.1, 575.1	B
240		542.2215	543.1, 545.1	B
241		525.1950	526.0, 528.0	B
242		511.1793	512.0, 514.0	B

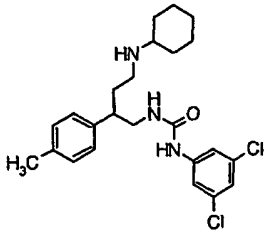
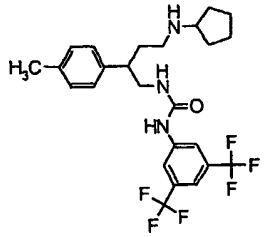
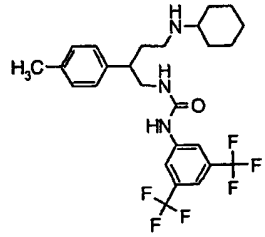
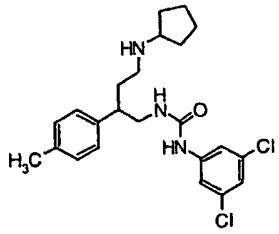
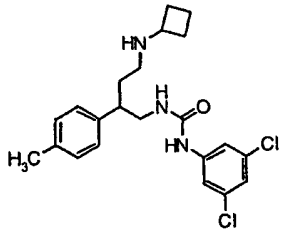
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
243		513.1750	514.1, 516.0	B
244		529.1454	530.0, 532.0, 534.0	B
245		563.1064	564.0, 566.0, 568.0, 570.0	B
246		546.1720	547.0, 549.0	B
247		580.1330	581.0, 583.0, 585.0	B

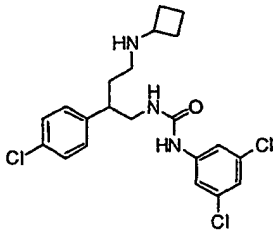
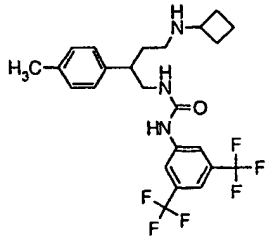
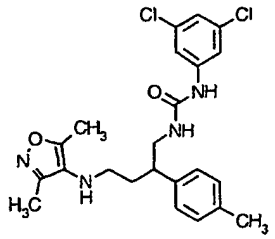
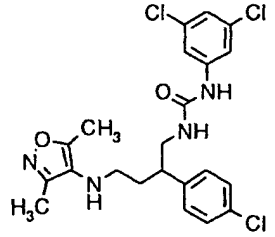
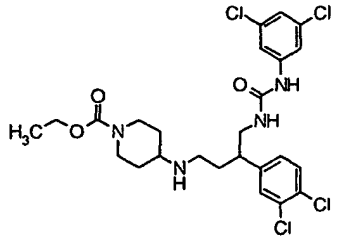
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
248		539.1742	540.1, 542.1	B
249		509.2000	510.1, 512.1	B
250		563.1718	564.0, 566.0	B
251		528.2058	529.1, 531.1	B
252		542.2215	543.1, 545.1	B

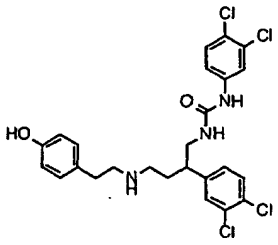
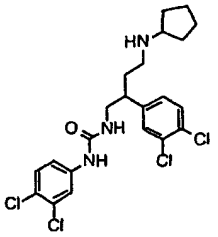
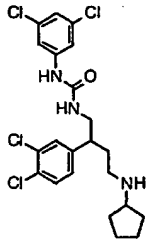
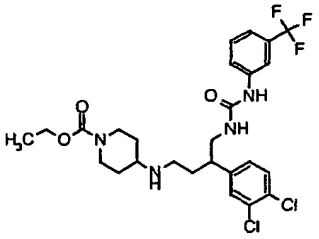
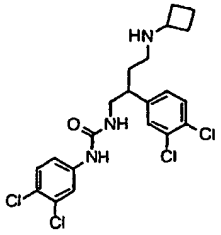
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
253		631.1591	632.1, 634.1	C
254		526.2266	527.1, 529.1	C
255		580.1983	581.0, 583.1	C
256		648.1857	649.1, 651.1	C
257		602.2426	603.1, 605.1, 606.1	C

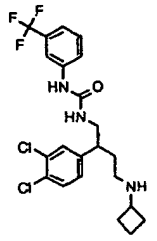
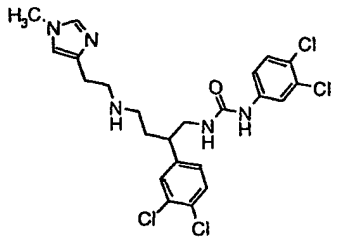
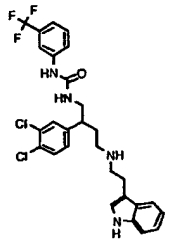
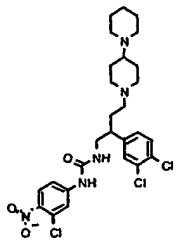
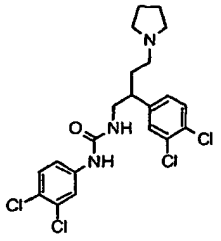
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
258		552.2234	555.0, 557.0, 558.0, 559.1	B
259		599.0912	597.9, 599.9, 602.0	B
260		558.1367	559.0, 561.0	B
261		537.0789	537.8, 539.9, 541.8	B
262		542.1663	543.0, 545.0	B

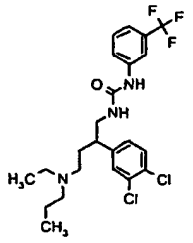
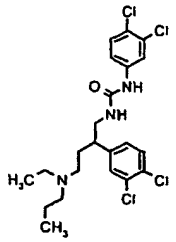
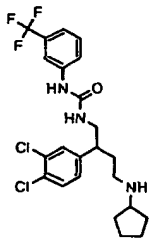
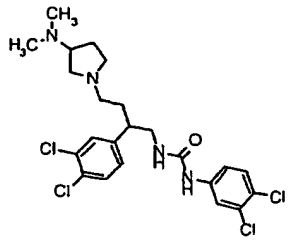
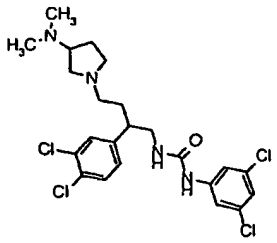
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
263		457.0890	457.9, 459.9, 462.0	C
264		569.1607	570.0, 572.0	C
265		441.1186	442.0, 444.0	C
266		467.1298	468.1, 470.1	B
267		453.1141	454.0, 456.0	B

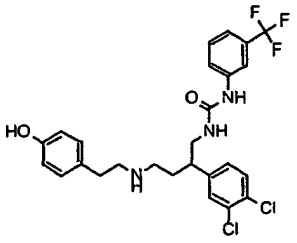
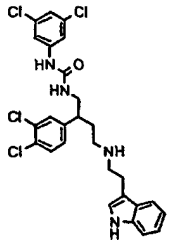
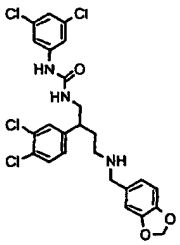
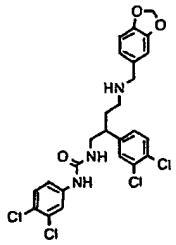
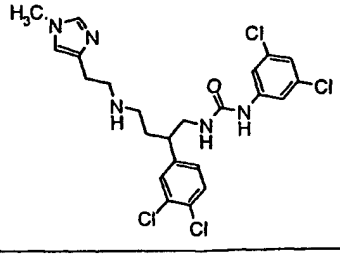
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
268		447.1844	448.0, 450.2	B
269		501.2214	502.2	B
270		515.2371	516.1	B
271		433.1687	434.0, 436.1	B
272		419.1531	420.0, 422.1	B

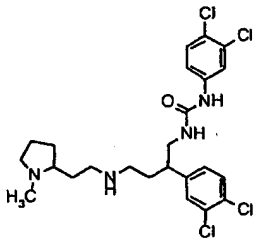
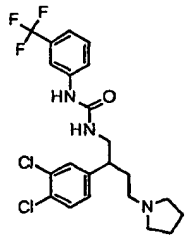
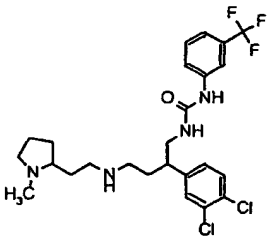
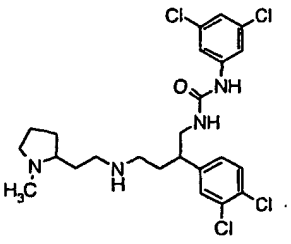
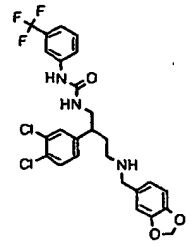
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
273		439.0985	440.0, 442.0	B
274		487.2058	488.1	B
275		460.1432	460.8, 462.9	C
276		480.0886	480.7, 482.9	C
277		574.1072	575.0, 576.9, 579.0	B

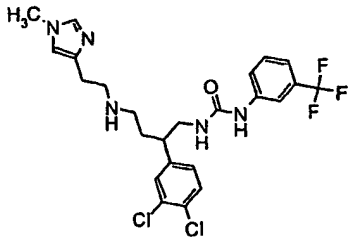
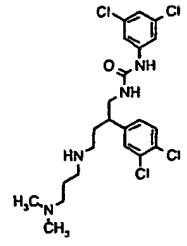
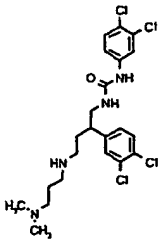
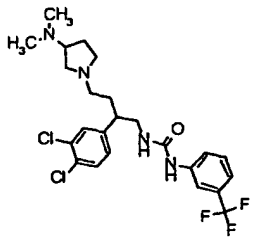
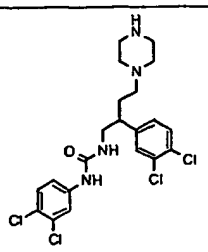
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
278		539.0701	540.0, 541.9, 544.0	B
279		487.0751	488.0, 490.0, 492.0	B
280		487.0751	487.9, 490.0, 491.9	B
281		574.1725	575.0, 577.0	B
282		473.0595	475.9, 479.1	B

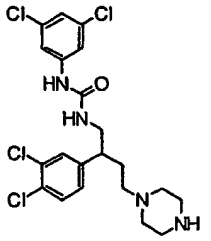
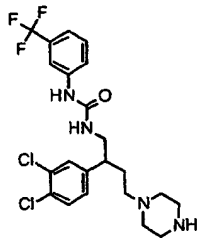
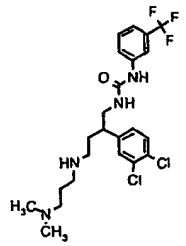
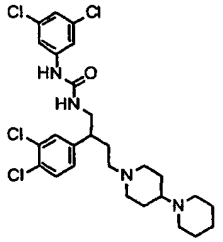
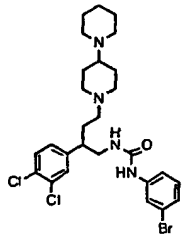
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
283		473.1248	474.1, 476.1	B
284		527.0813	528.0, 530.0, 531.9	B
285		562.1514	563.0, 565.0	B
286		581.1727	582.1, 584.1, 586.1	B
287		473.0595	474.0, 476.0, 478.0	B

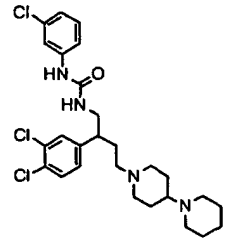
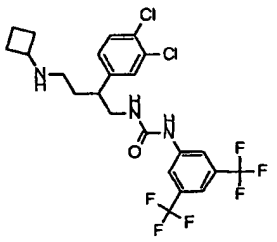
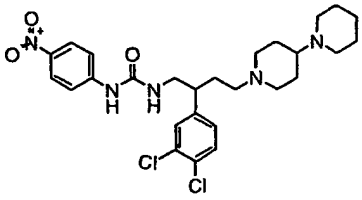
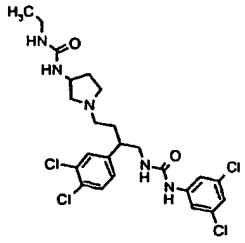
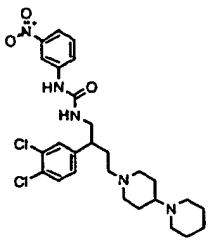
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
288		489.1561	490.0, 492.0	B
289		489.0908	492.0, 494.1	B
290		487.1405	488.0, 490.1	B
291		516.1017	517.1, 519.0, 521.0	B
292		516.1017	517.0, 519.0, 521.0	B

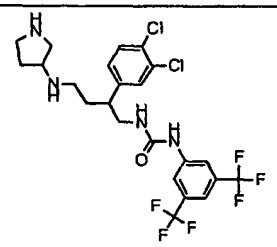
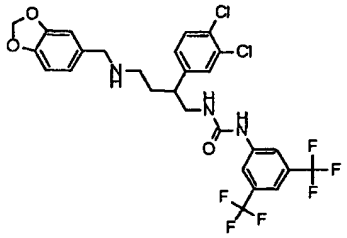
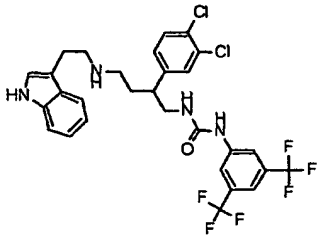
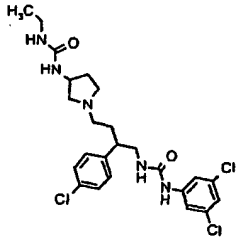
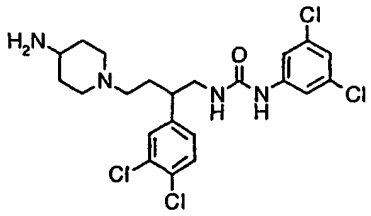
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
293		539.1354	540.0, 541.9	B
294		562.0860	563.1, 565.0, 567.0	C
295		553.0493	553.8, 555.8, 557.8	C
296		553.0493	553.9, 555.9	C
297		527.0813	528.0, 530.0, 531.9	C

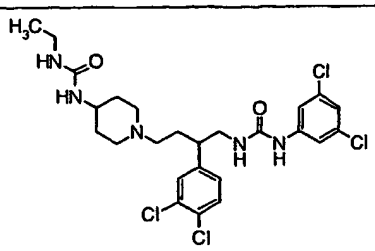
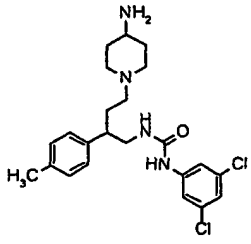
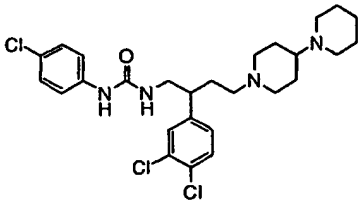
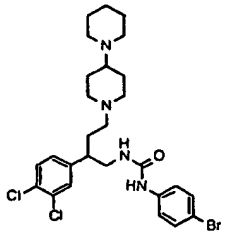
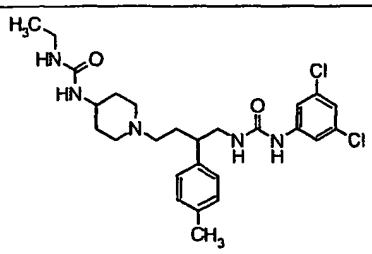
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
298		530.1173	530.9, 533.0, 535.0	C
299		473.1248	474.1, 476.0	C
300		530.1827	531.1, 533.1	C
301		530.1173	531.0, 532.9, 535.1	C
302		553.1146	553.9, 555.9	C

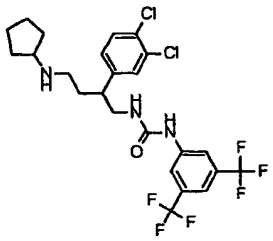
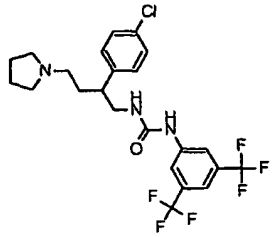
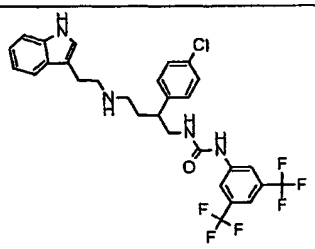
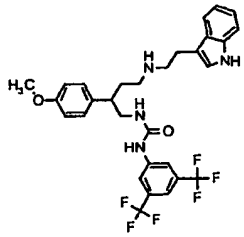
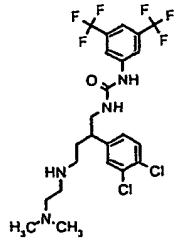
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
303		527.1466	528.1, 530.0	C
304		504.1017	505.0, 506.9	C
305		504.1017	505.0, 507.0, 509.0	C
306		516.1670	517.0, 519.1	C
307		488.0704	489.0, 491.0, 493.1	C

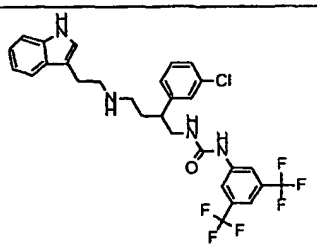
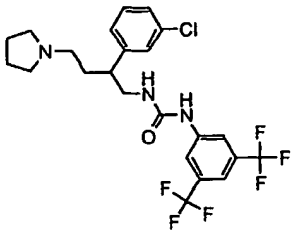
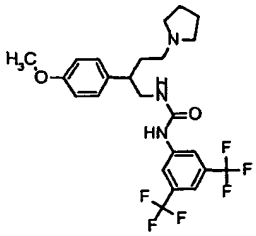
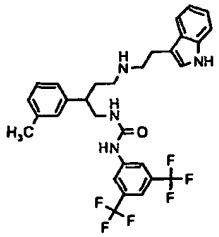
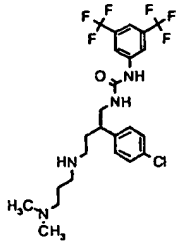
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
308		488.0704	489.0, 491.0, 493.1	C
309		488.1357	489.0, 491.1	C
310		504.1670	505.1, 507.0	C
311		570.1486	571.0, 573.1, 575.1	B
312		580.1371	581.0, 583.0, 585.0	B

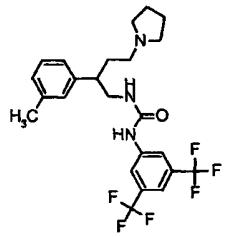
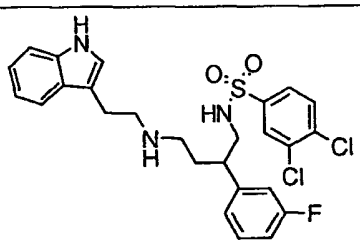
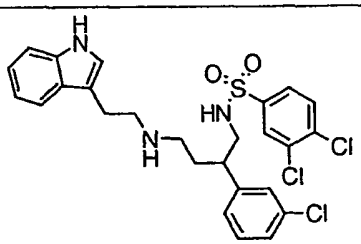
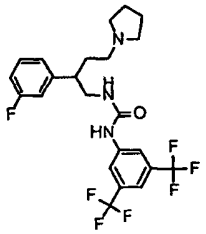
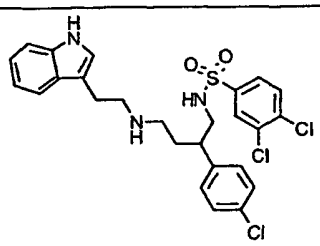
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
313		536.1876	560.0, 562.0, 564.0	B
314		541.1122	542.8, 544.8	B
315		547.2117	548.1, 550.0, 551.1	B
316		559.1075	560.0, 562.0, 564.1	C
317		547.2117	548.1, 550.1	C

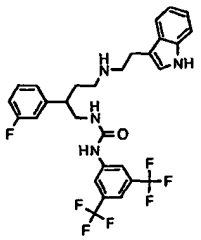
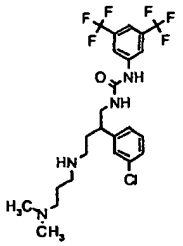
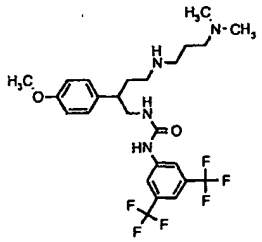
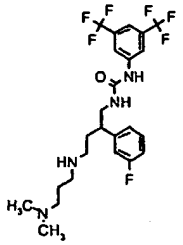
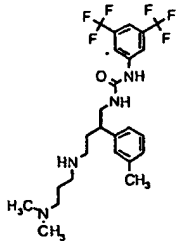
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
318		556.1231	556.9, 559.1	C
319		621.1020	621.8, 623.8	C
320		630.1387	631.0, 632.9, 634.0	C
321		525.1465	526.0, 528.0	C
322		502.0860	503.0, 505.0, 507.1	C

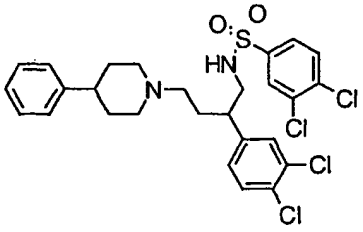
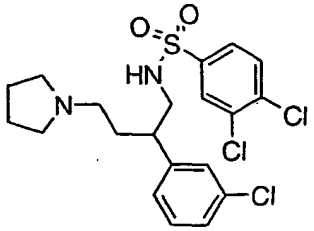
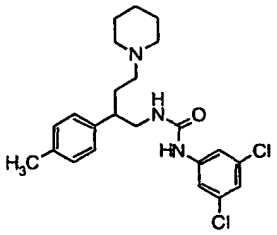
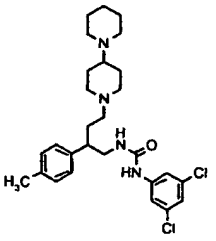
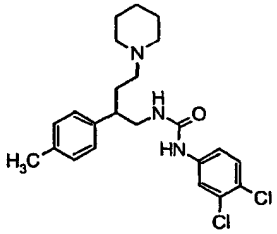
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
323		573.1231	574.0, 576.0	C
324		448.1796	449.1, 451.1	C
325		536.1876	537.0, 539.0	C
326		580.1371	581.0, 583.0, 585.0	C
327		519.2167	520.1, 522.1	C

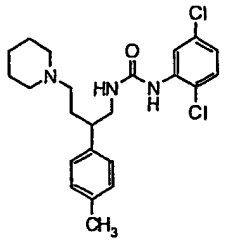
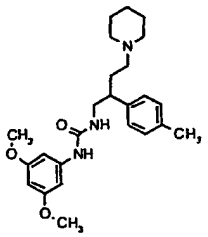
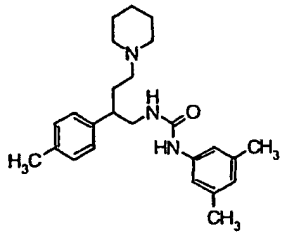
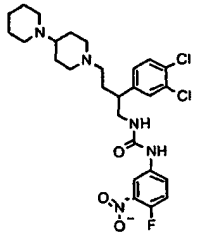
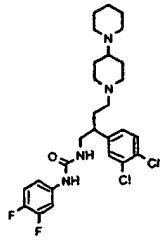
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
328		555.1278	556.1, 558.1	A
329		507.1512	508.2, 510.2	B
330		596.1777	597.1, 599.1	B
331		592.2272	593.1	B
332		558.1387	559.0, 561.0	B

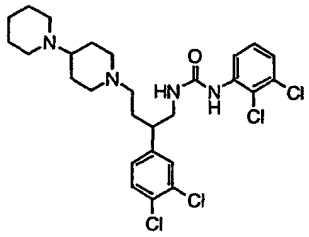
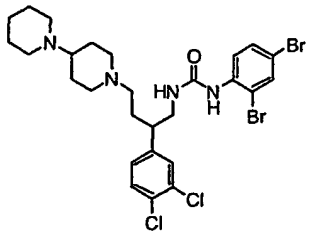
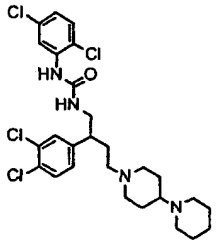
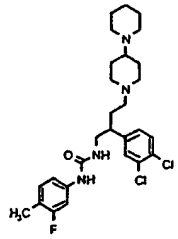
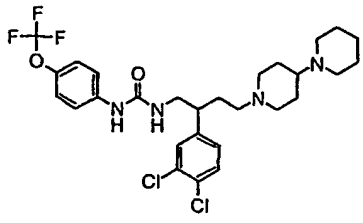
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
333		596.1777	597.1, 599.1	B
334		507.1512	508.2, 510.1	C
335		503.2007	504.2	C
336		576.2323	577.1	C
337		538.1934	539.1, 541.1	C

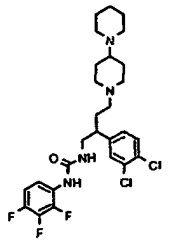
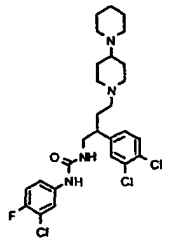
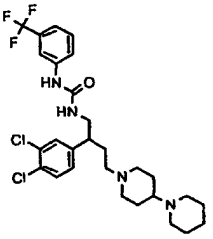
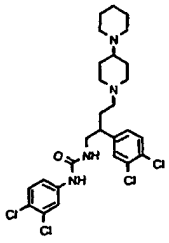
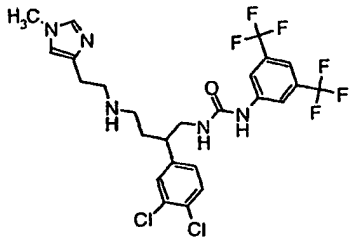
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
338		487.2058	488.2	C
339		533.1106	534.0, 535.9	C
340		549.0811	549.9, 551.9, 553.0	C
341		491.1807	492.2	C
342		549.0811	552.0, 554.0	C

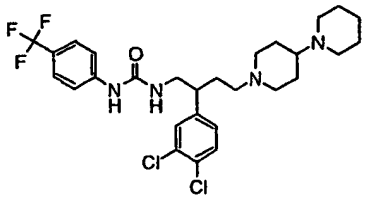
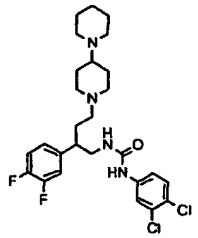
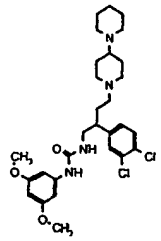
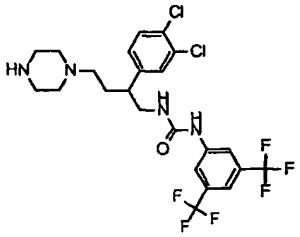
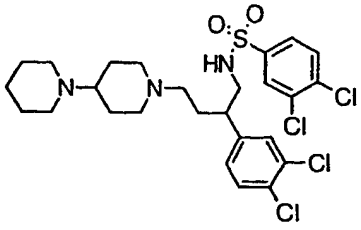
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
343		580.2073	581.1	C
344		538.1934	539.1	C
345		534.2429	535.1	C
346		522.2229	523.2	C
347		518.2480	519.2	C

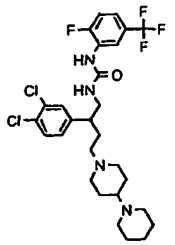
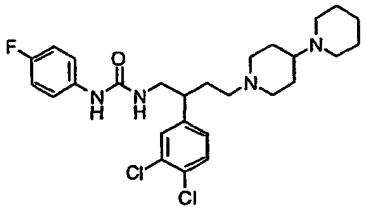
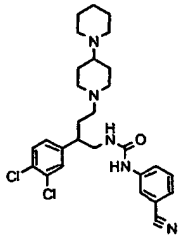
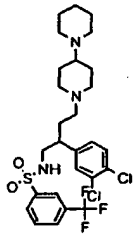
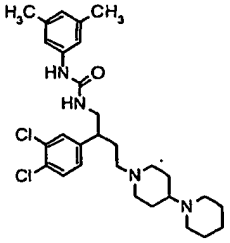
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
348		584.0625	585.1, 587.1, 589.1, 591.2	C
349		460.0546	461.1, 463.1, 465.1	C
350		433.1687	434.2, 436.2	B
351		516.2422	517.2, 519.1	B
352		433.1687	434.2, 436.2	B

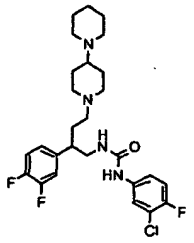
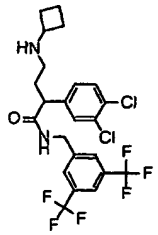
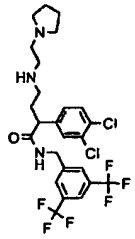
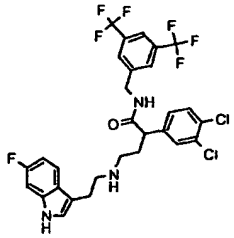
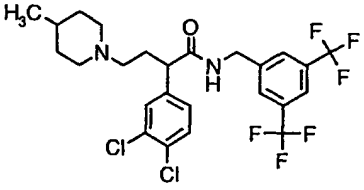
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
353		433.1687	434.1, 436.1	B
354		425.2678	426.2	C
355		393.2780	394.2	C
356		565.2022	566.1, 568.2	B
357		538.2077	539.1, 541.1	B

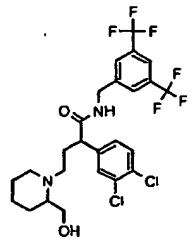
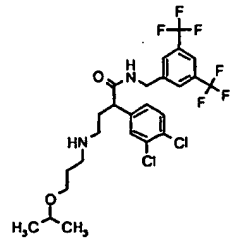
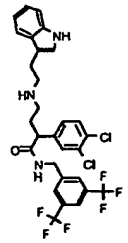
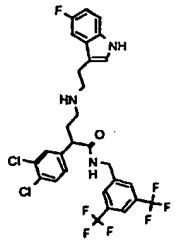
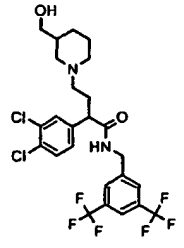
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
358		570.1486	571.1, 573.1, 575.1	C
359		658.0475	659.0, 661.0, 663.0, 665.0	C
360		570.1486	571.1, 573.1, 575.1	C
361		534.2328	535.2, 537.1	C
362		586.2089	587.2, 589.1	C

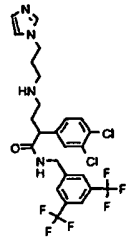
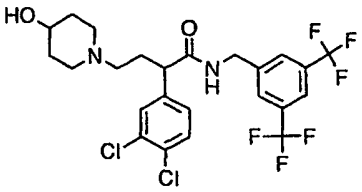
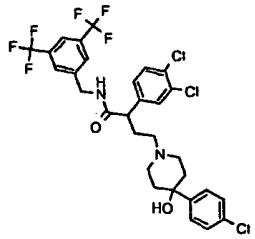
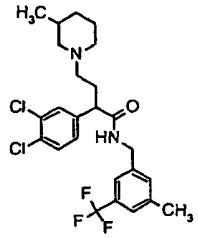
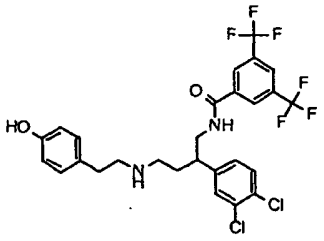
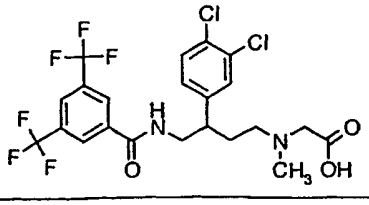
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
363		556.1983	557.2, 559.2	C
364		554.1782	555.1, 557.1, 559.1	B
365		570.2140	571.2, 573.2	B
366		570.1486	571.1, 573.2	B
367		595.1340	596.1, 598.1	C

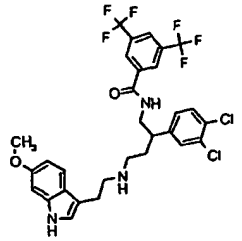
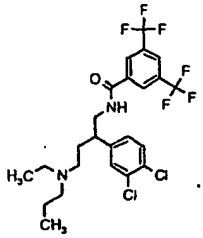
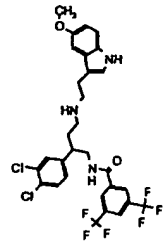
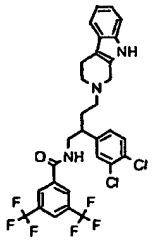
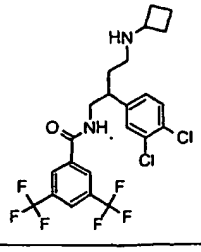
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
368		570.2140	571.2, 573.1	C
369		538.2077	539.1, 541.1	C
370		562.2477	563.2, 565.1	C
371		556.1231	557.1, 559.1	C
372		591.1047	592.1, 594.1, 596.0	C

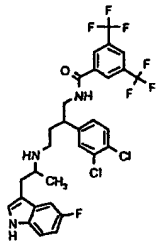
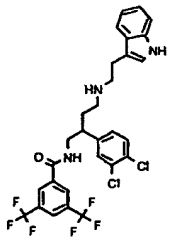
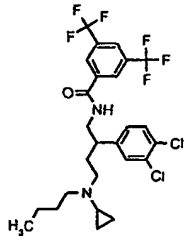
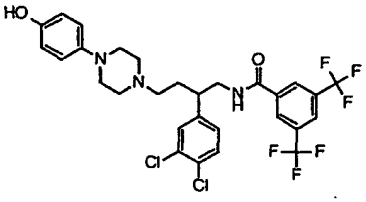
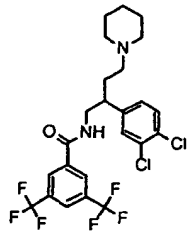
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
373		588.2045	589.1, 591.0, 593.1	C
374		520.2172	521.2, 523.1	C
375		527.2218	528.2, 530.1	C
376		591.1700	592.1, 594.1	C
377		530.2579	531.2, 533.2	C

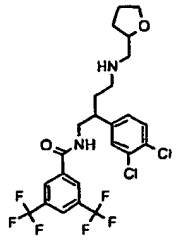
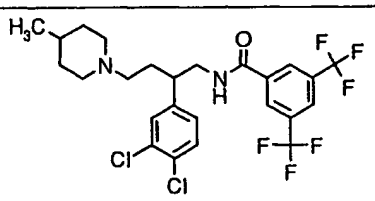
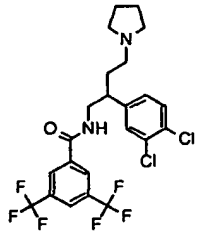
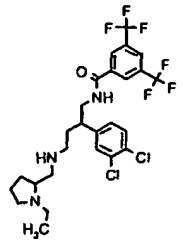
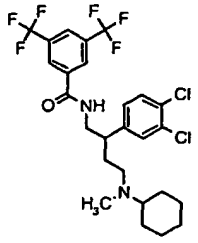
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
378		522.2373	523.2, 524.3	C
379		526.1013	527.0, 529.0	C
380		569.1435	570.0, 572.1	C
381		633.1184	634.0, 636.0	C
382		554.1326	555.0, 557.1	C

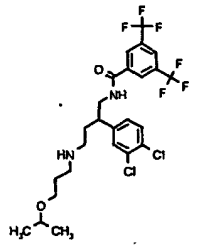
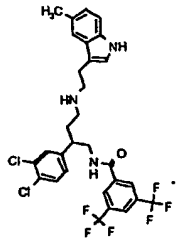
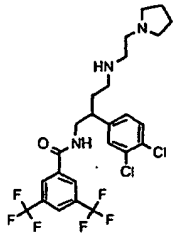
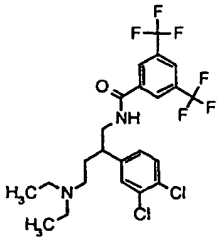
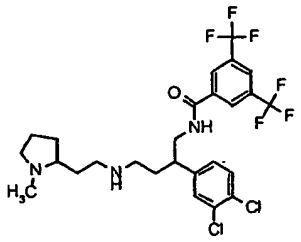
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
383		570.1275	571.1, 573.1	C
384		572.1432	573.1, 575.1	C
385		615.1278	616.0, 618.0	C
386		633.1184	634.0, 635.9	C
387		570.1275	571.1, 573.1	C

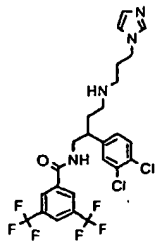
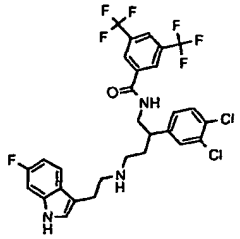
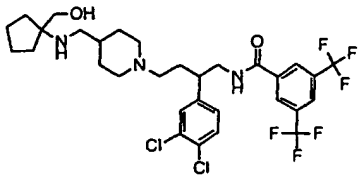
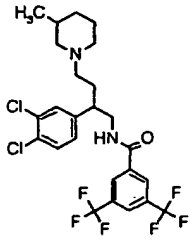
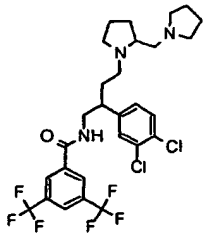
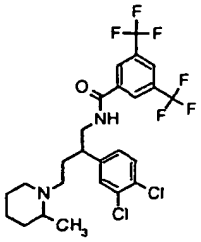
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
388		580.1231	581.1, 583.1	C
389		556.1119	557.1, 559.1	C
390		666.1042	667.0, 669.0	C
391		500.1609	501.1, 503.1	C
392		592.1119	593.1, 595.0	B
393		544.0755	545.0, 547.0	C

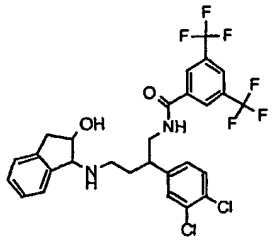
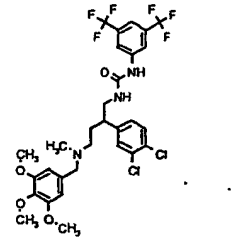
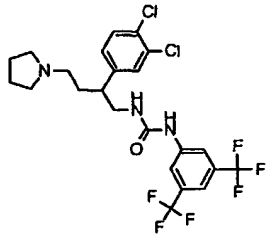
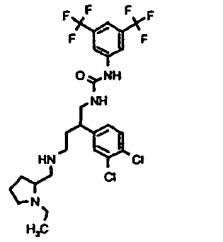
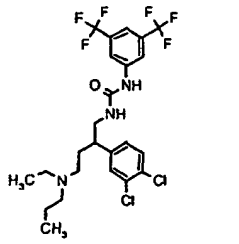
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
394		645.1384	645.9, 648.1	C
395		542.1326	543.1, 545.0	C
396		645.1384	646.0, 648.1	C
397		627.1278	628.0, 629.9	C
398		526.1013	527.1, 529.0	C

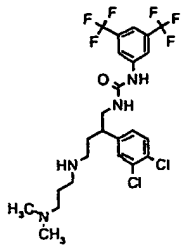
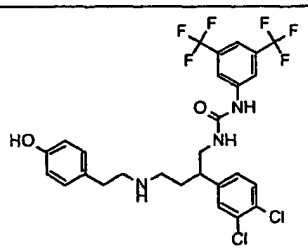
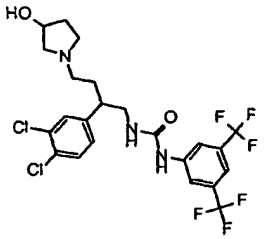
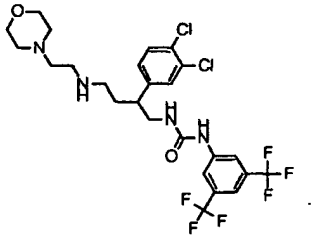
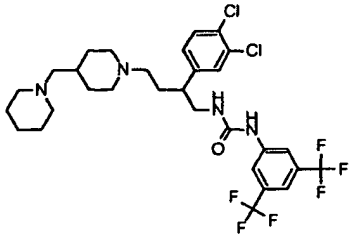
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
399		647.1341	648.0, 650.0	C
400		615.1278	616.0, 618.0	C
401		568.1482	569.1, 571.1	C
402		633.1384	634.2, 636.1	C
403		540.1169	541.1, 543.1	C

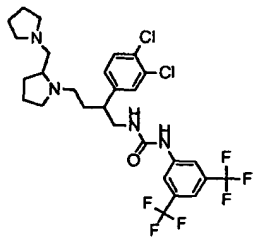
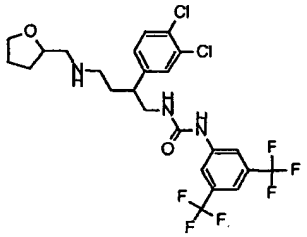
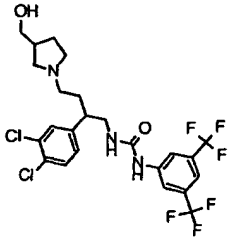
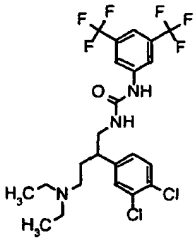
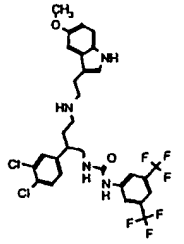
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
404		556.1119	557.1, 559.1	C
405		554.1326	555.2, 557.1	C
406		526.1013	527.1, 529.1	C
407		583.1591	584.1, 586.0	C
408		568.1482	569.1, 571.1	C

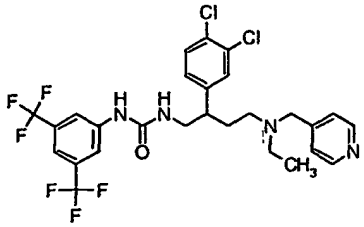
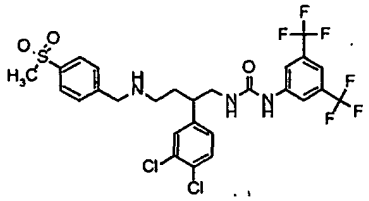
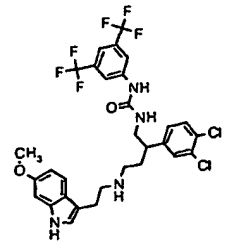
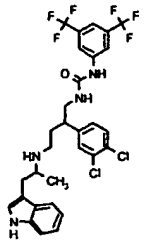
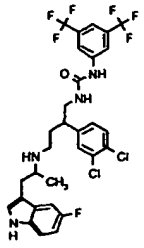
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
409		572.1432	573.1, 575.1	C
410		629.1435	630.0, 632.1	C
411		569.1435	570.1, 572.1	C
412		528.1169	529.1, 531.0	C
413		583.1591	584.1, 586.1	C

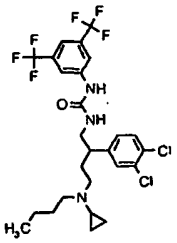
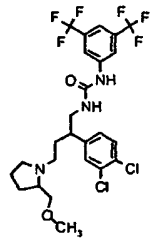
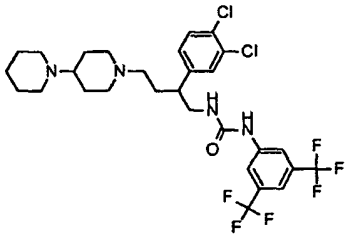
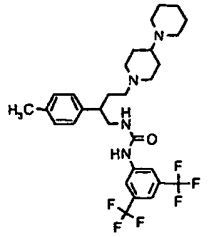
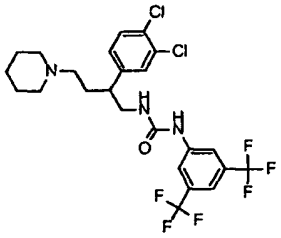
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
414		580.1231	581.1, 583.1	C
415		633.1184	634.1, 636.0	C
416		667.2167	668.0, 670.1	C
417		554.1326	555.2, 557.1	C
418		609.1748	610.0, 612.1	C
419		554.1326	555.1, 557.2	C

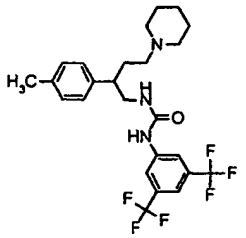
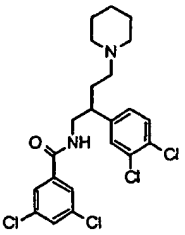
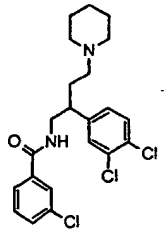
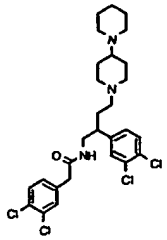
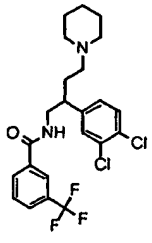
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
420		604.1119	605.0. 607.0	C
421		681.1595	681.9, 683.9	B
422		541.1122	542.1, 544.1	B
423		598.1700	599.1, 601.1	B
424		557.1435	558.1, 560.1	C

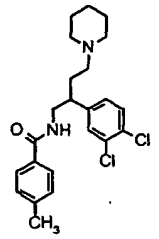
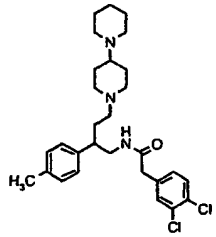
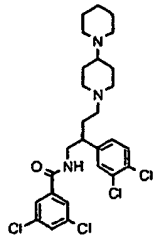
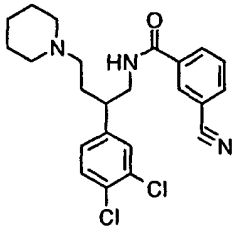
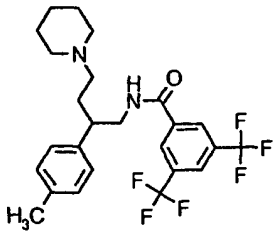
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
425		572.1544	573.1, 575.1	C
426		607.1228	608.1, 610.1	C
427		557.1071	558.1, 560.1	C
428		600.1493	601.1, 603.0	C
429		652.2170	653.1, 655.1	C

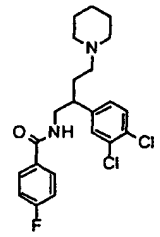
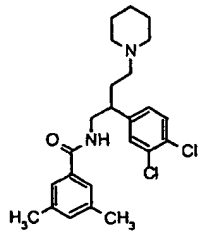
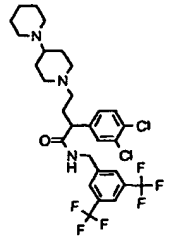
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
430		624.1857	625.1, 627.1	C
431		571.1228	572.1, 574.0	C
432		571.1228	572.2, 574.1	C
433		543.1278	544.1, 546.1	C
434		660.1493	661.1, 663.1	C

Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
435		606.1387	607.1, 609.0	C
436		655.0897	656.0, 658.0	C
437		660.1493	661.0, 663.0	C
438		644.1544	645.0, 647.1	C
439		662.1450	663.0, 665.0	C

Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
440		583.1591	584.2, 586.1	C
441		585.1384	586.2, 586.1	C
442		638.2013	639.2, 641.1	B
443		584.2949	585.2	B
444		555.1278	556.2, 558.1	B

Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
445		501.2214	502.2	C
446		472.0642	473.1, 475.1, 477.2	C
447		438.1032	439.1, 441.1, 443.1	C
448		569.1534	570.0, 572.1, 574.0	C
449		472.1296	473.2, 475.1	C

Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
450		418.1578	419.1, 421.1	C
451		515.2470	516.2, 518.1	C
452		555.1377	556.1, 558.2	C
453		429.1374	430.2, 432.1	C
454		486.2105	487.2	C

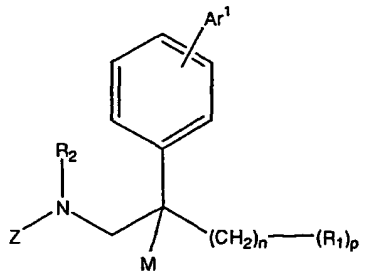
Example	Chemistry	Exact MS, calc.	MS (ESI) found	Activity
455		422.1328	423.1, 425.1	C
456		432.1735	433.1, 435.1	C
457		623.1904	624.1	C

5

CLAIMS

What is claimed is:

1. A compound, including enantiomers, stereoisomers, rotamers, tautomers and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound or of said prodrug, said compound having the general structure shown in Formula I:



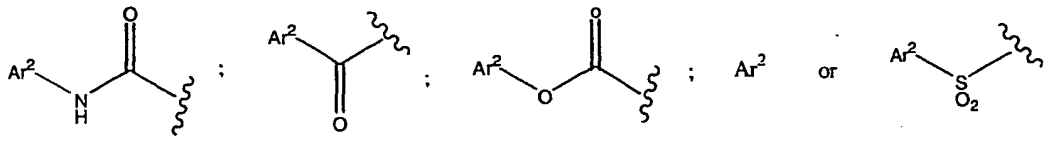
Formula I

wherein:

Ar^1 = unsubstituted or substituted phenyl, pyridine, pyridine-N-oxide, pyrazine or pyridazine, wherein the substituents number from 0 to 5, may be the same or different and are independently selected from the group consisting of H, CN, OCF_3, F, Cl, Br, I, $CONH_2$, methylenedioxy, OR, CO_2H, CO_2R, and OH with R being a C_1-C_6 straight chain alkyl or branched alkyl or a C_3-C_7 cycloalkyl;

M is H or R;

Z =

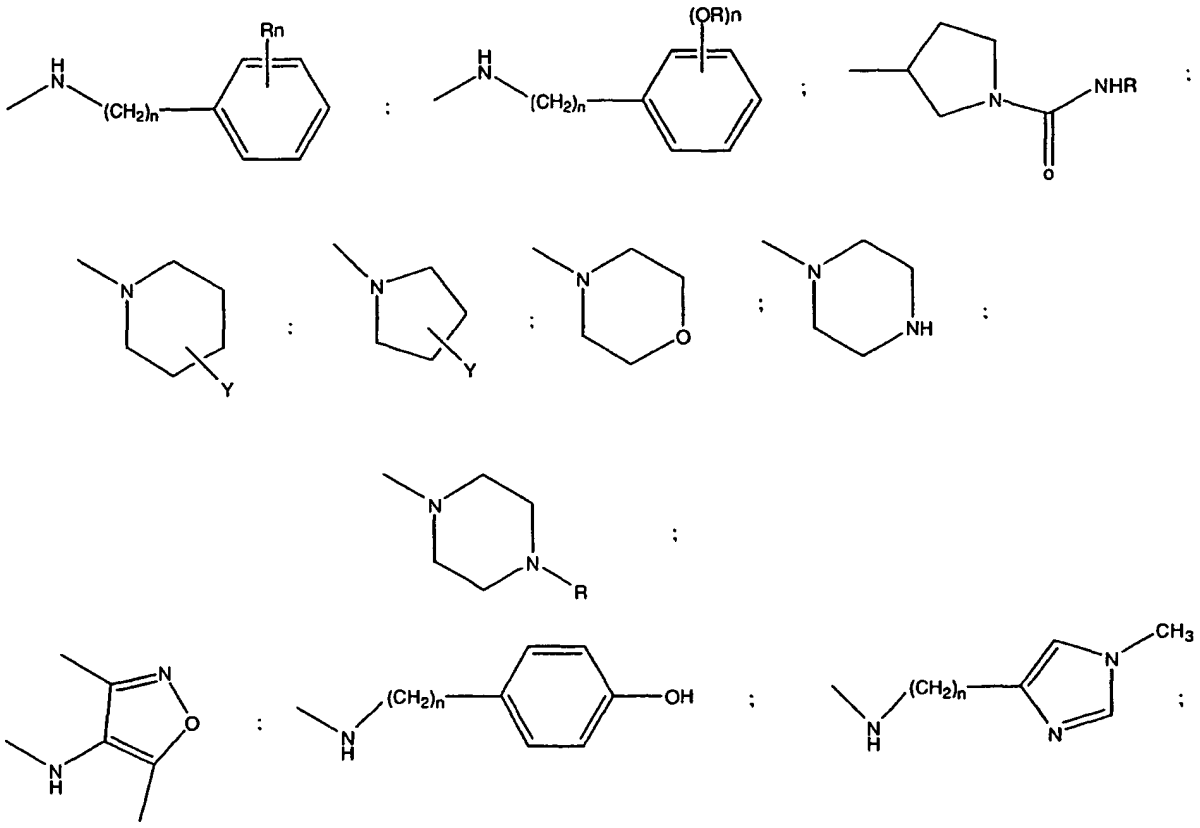


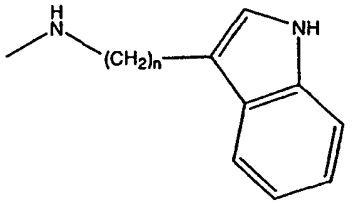
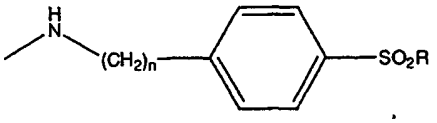
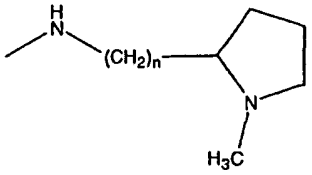
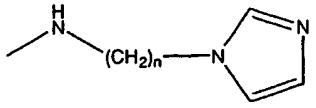
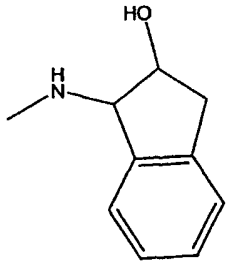
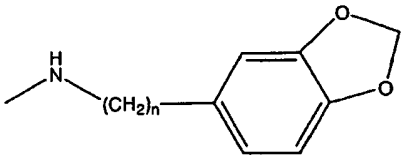
where Ar^2 is an unsubstituted or substituted phenyl wherein the substituents number from 0 to 5, may be the same or different and are independently selected from the group consisting F, Cl, Br, I, R, OR, NO_2, and CF_3;

n = 0 to 6;

p = 1-6;

R_1 may be the same or different and is independently selected from the group consisting of R; NH_2; NHR; $N(R)_2$; $N(R)_2 \rightarrow O$; $NH(CH_2)_nOR$; $N(R)SO_2R$; $NH(CH_2)_n$-$N(R)_2$; $N(R)SO_2(R)$;

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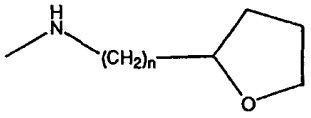
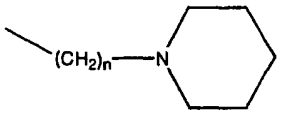
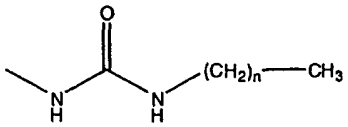
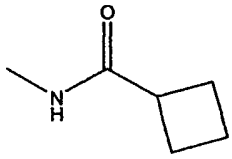
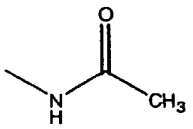
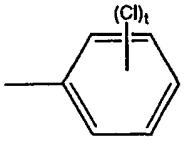
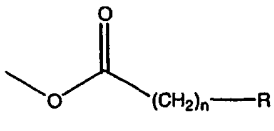
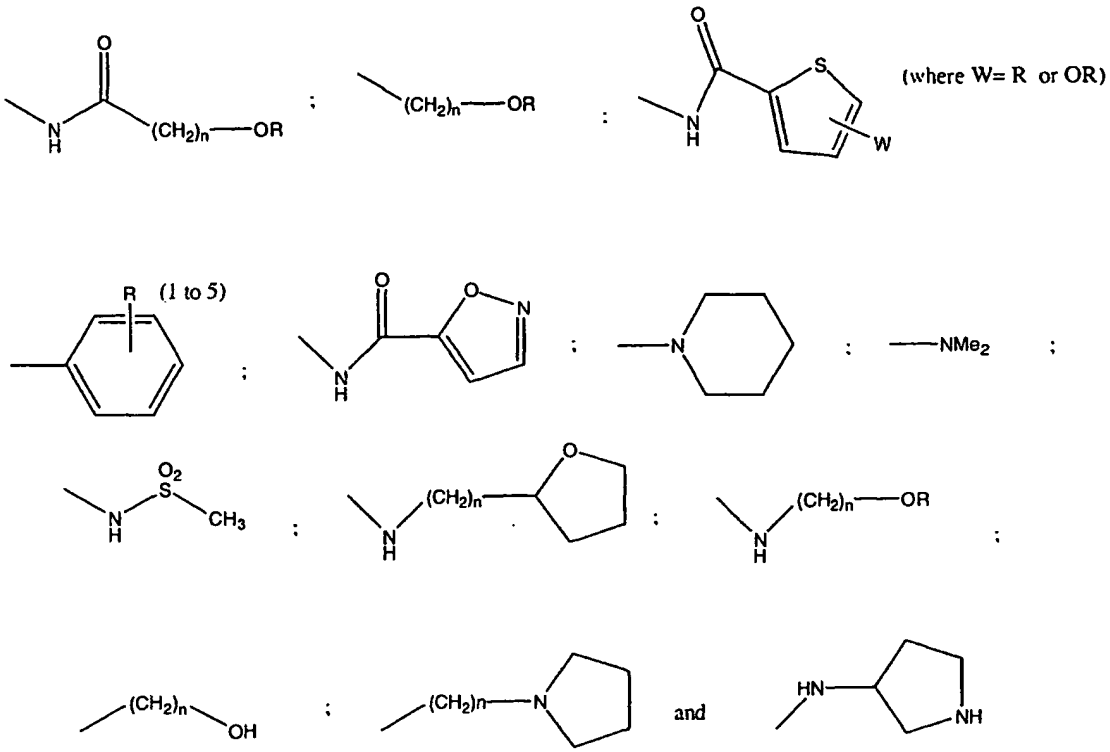


where n is defined above and where Y is a moiety numbering 0 to 5 which may be the same or different and are independently selected from the group consisting of H; OH; NH_2;



where n is defined above and t = 1 to 5;

and R_2 is H or alkyl.

2. The compound of claim 1, wherein M is H.

3. The compound of claim 1, wherein Ar^1 is 4-phenyl.

4. The compound of claim 1, wherein Ar^1 is 4-pyridyl.

5. The compound of claim 3, wherein said phenyl is substituted on the ring with at least one of CN, OCF_3, F and Cl or combinations thereof.

6. The compound of claim 3, wherein said substituents are in position 3 on the ring with respect to said ring's attachment to the benzylic position in Formula I.

7. The compound of claim 4, wherein said pyridyl is substituted on the ring with at least one of CN, OCF_3, F and Cl or combinations thereof.

8. The compound of claim 1, wherein Z is Ar^2-NH-CO, where Ar^2 is phenyl.

9. The compound of claim 8, wherein said phenyl is substituted with one or more moieties which number 0 to 5, may be the same or different and are independently selected from the group consisting of F, Cl, Br, I, OCH_3, and CF_3.

10. The compound of claim 9, wherein said substituent on Ar^2 is F, Cl or OCH_3.

11. The compound of claim 1, wherein R is a C_1-C_4 straight chain alkyl, a C_1-C_4 branched alkyl or a C_3-C_7 cycloalkyl.

12. The compound of claim 11, wherein R is methyl, ethyl or propyl.

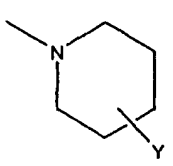
13. The compound of claim 11, wherein R is isopropyl.

14. The compound of claim 11, wherein R is cyclobutyl.

15. The compound of claim 1, wherein n is 2-4.

16. The compound of claim 1, wherein n is 2.

17. The compound of claim 1, wherein R_1 is selected from the group consisting of NH_2; NHR; $N(R)_2$; $N(R)_2 \longrightarrow O$; $NH(CH_2)_nOCH_3$; $N(R)SO_2R$; $NH(CH_2)_n$-$N(R)_2$; $N(R)SO_2(R)$;



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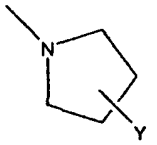

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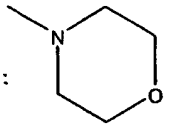

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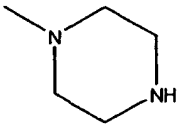
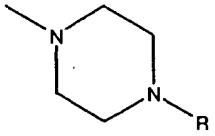
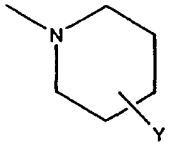


: and



with R and Y defined in Claim 1.

18. The compound of claim 17, wherein R_1 is selected from the group consisting of NHMe; NHEt; NMe_2; $NH(CH_2)_nOCH_3$; NH-cyclopropyl; NH-cyclobutyl; NH-cyclopentyl; $NH(CH_2)_3NMe_2$;



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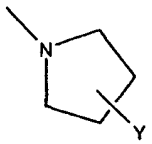
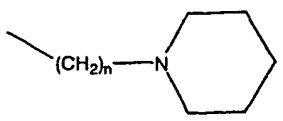


19. The compound of claim 1, wherein Y is selected from the group consisting of NH_2; NMe_2; NHMe;



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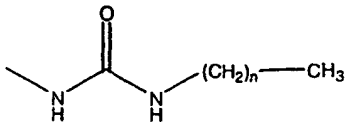

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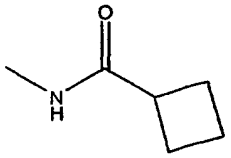
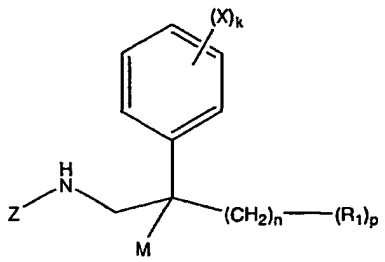


20. A compound, including enantiomers, stereoisomers, rotamers, tautomers and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound or of said prodrug, said compound having the general structure shown in Formula II:



Formula II

wherein:

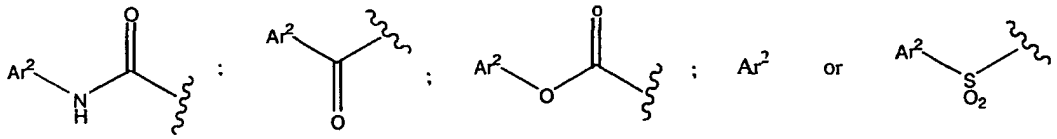
M is H or R;

k = 0 to 5;

p = 1 to 6;

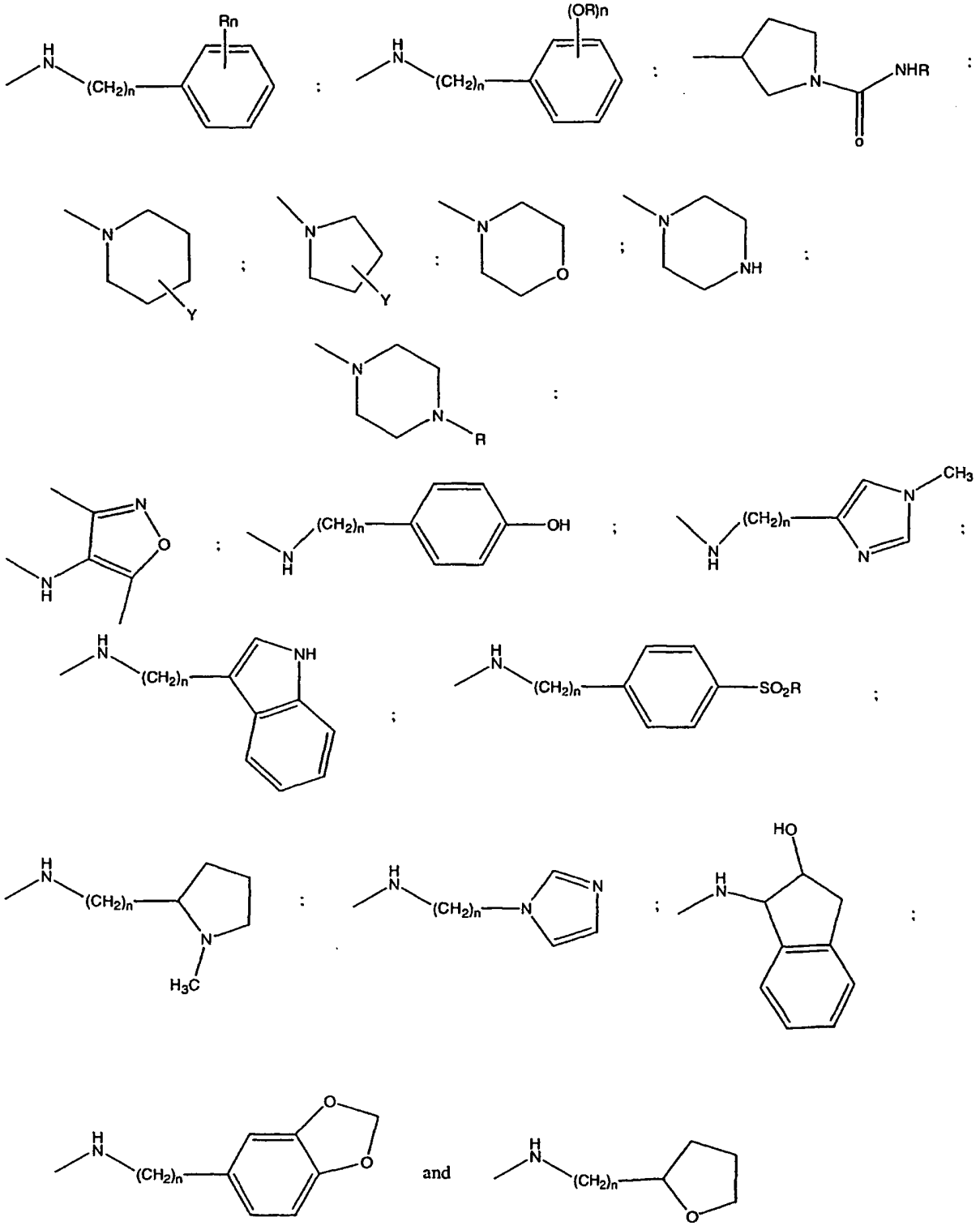
n = 0 to 6;

Z =



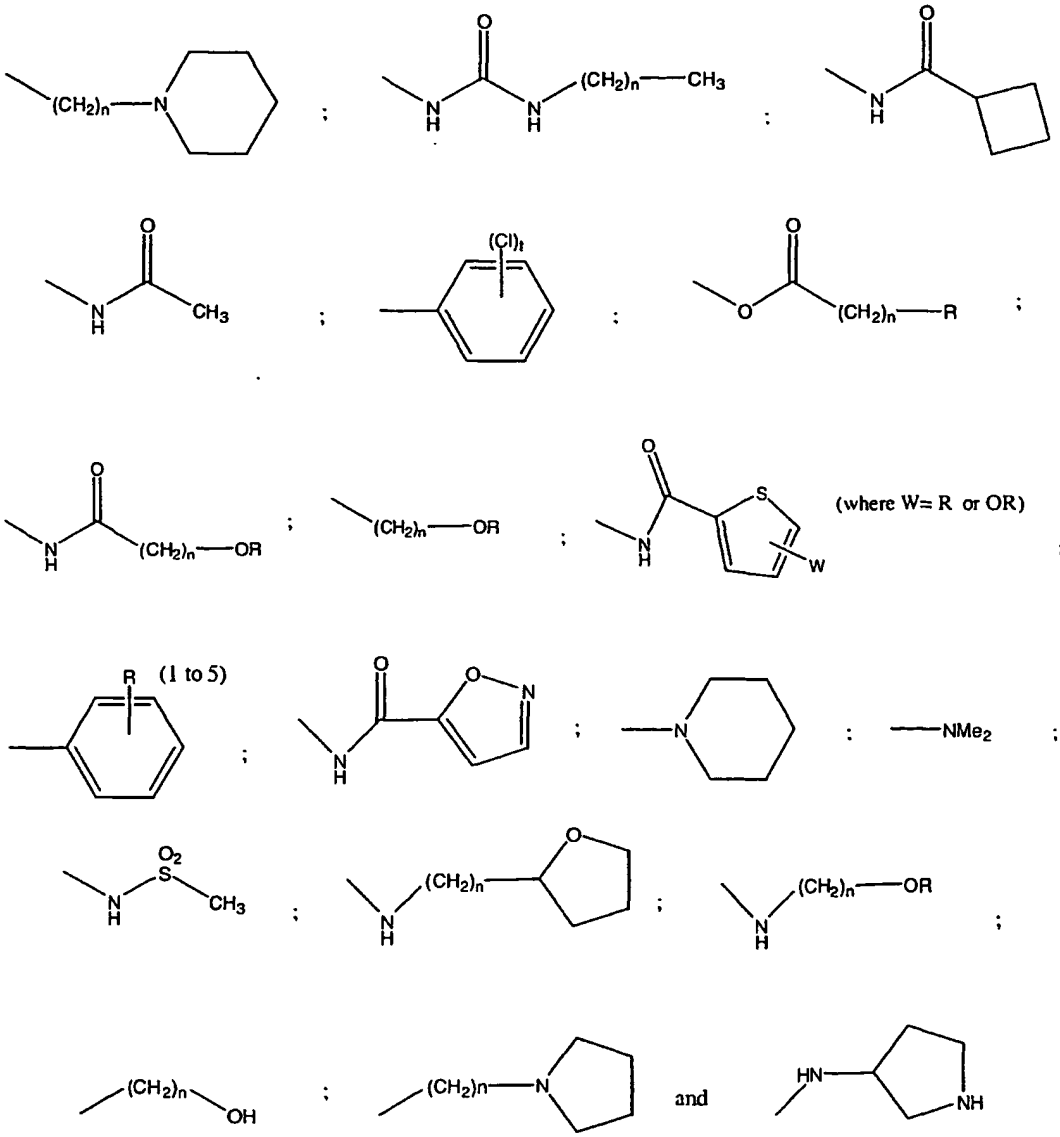
where Ar^2 is an unsubstituted or substituted phenyl with said substituents numbering 0 to 5 which may be the same or different and are independently selected from the group consisting of F, Cl, Br, I, R, OR, NO_2, and CF_3;

R_1 may be the same or different and are independently selected from the group consisting of R; NH_2; NHR; $N(R)_2$; $N(R)_2 \longrightarrow O$; $NH(CH_2)_nOR$; $N(R)SO_2R$; $NH(CH_2)_n$-$N(R)_2$; $N(R)SO_2(R)$;



and

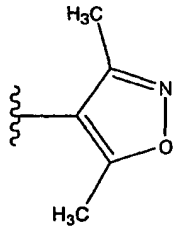
where n and R are defined above and Y is a moiety numbering 0 to 5 which may be the same or different and are independently selected from the group consisting of H; OH; NH_2;



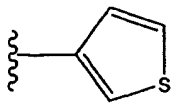
where n is defined above and t = 1 to 5; and

X may be the same or different, and are independently selected from the group consisting of:

H, Cl, F, Br, I, R, OR, CF_3, OCF_3, methylenedioxy, phenyl,



and



21. The compound of claim 20, wherein k numbers 1-3.

22. The compound of claim 20, wherein X is selected from the group consisting of R, H, Cl, CF_3 and OCF_3 where R is as defined in claim 20.

23. The compound of claim 20 wherein M is H.

24. The compound of claim 20, wherein Z is Ar^2-NH-CO, where Ar^2 is phenyl.

25. The compound of claim 24, wherein said phenyl is substituted with one or more moieties which number 0 to 5, may be the same or different and are independently selected from the group consisting of F, Cl, Br, I, OCH_3, and CF_3.

26. The compound of claim 20, wherein R is a C_1-C_4 straight chain or branched alkyl.

27. The compound of claim 20, wherein n is 2.

28. A pharmaceutical composition comprising as an active ingredient at least one compound of claim 1 or claim 20.

29. The pharmaceutical composition of claim 28 for use in treating disorders associated with the MCH receptor.

30. The pharmaceutical composition of claim 28 additionally comprising a pharmaceutically acceptable carrier.

31. A method of treating disorders associated with the MCH receptor, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which composition comprises therapeutically effective amounts of at least one compound of claim 1 or of claim 20.

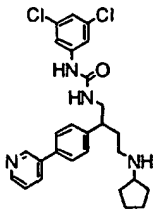
32. The method of claim 31, wherein said administration is oral.

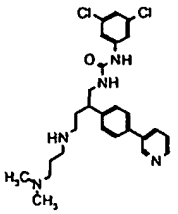
33. The method of claim 31, wherein said administration is via subcutaneous administration.

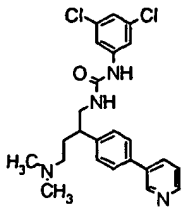
34. The use of a compound of claim 1 or claim 20 for the manufacture of a medicament to treat disorders associated with the MCH receptor.

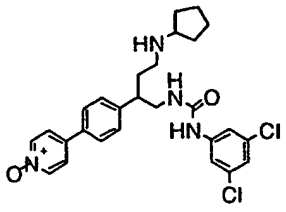
35. A method of preparing a pharmaceutical composition for treating disorders associated with the MCH receptor, said method comprising bringing into intimate contact at least one compound of a compound of claim 1 or of claim 20 and a pharmaceutically acceptable carrier.

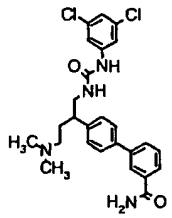
36. A compound exhibiting MCH modulatory activity, including enantiomers, stereoisomers, rotamers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the group of compounds with structures listed below:

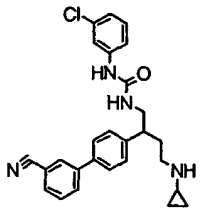


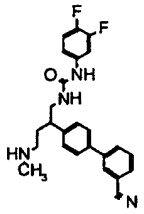


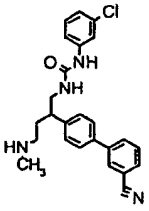


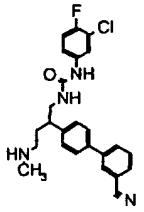


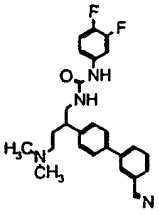


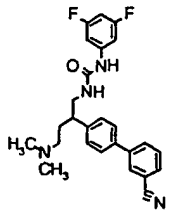


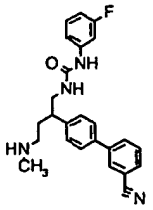


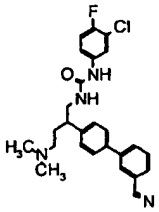


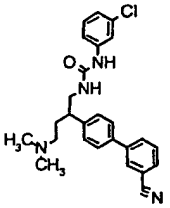


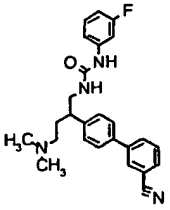












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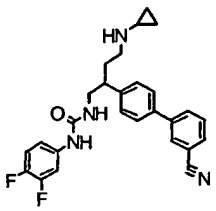

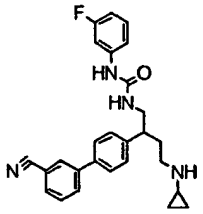

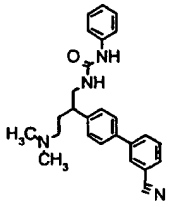

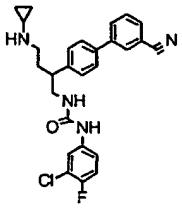

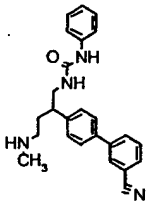

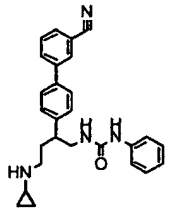

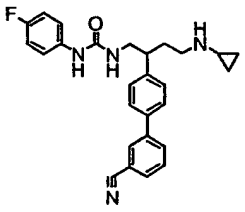

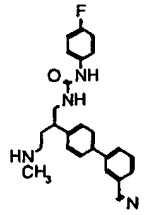

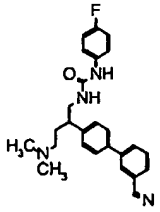

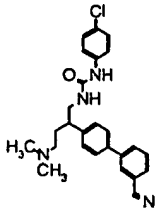

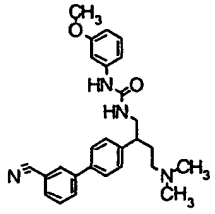

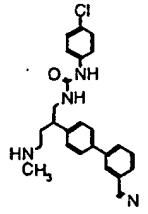

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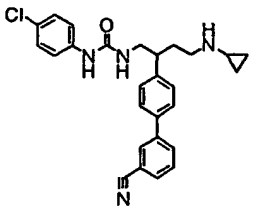

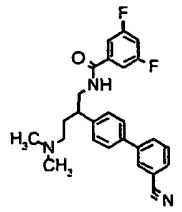

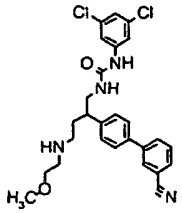

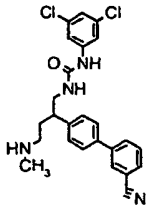

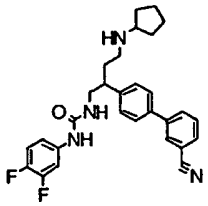

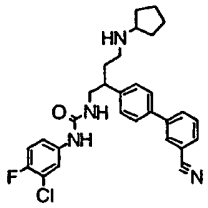

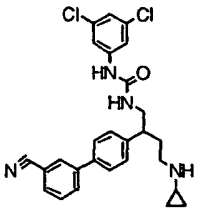

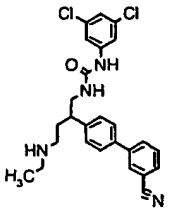

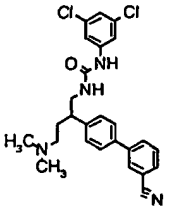

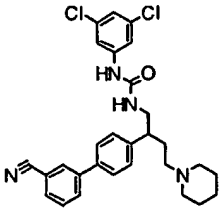

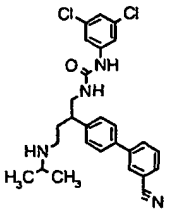

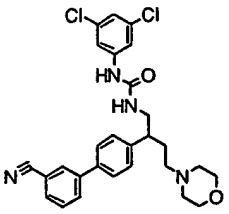

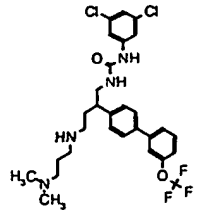

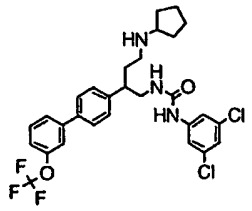

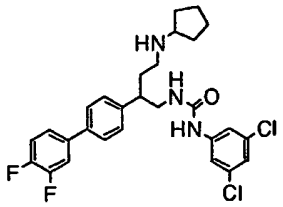

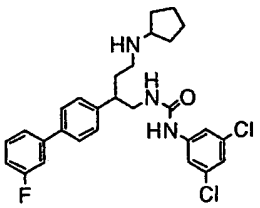

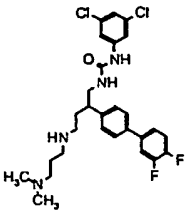

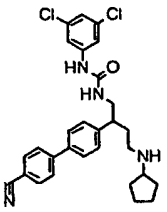

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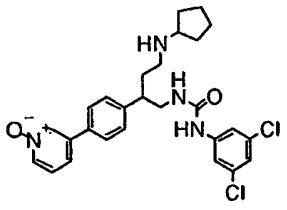

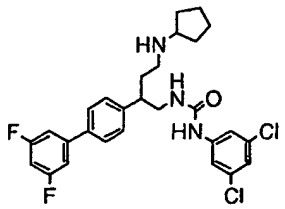

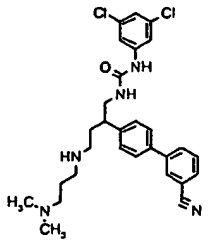

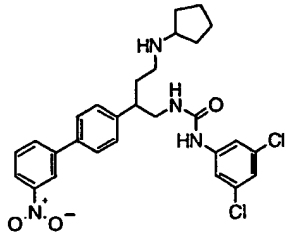

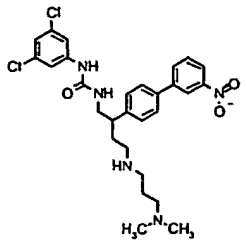

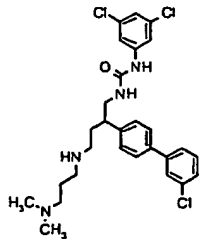

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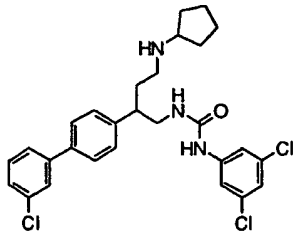
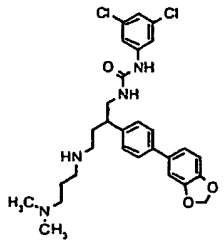
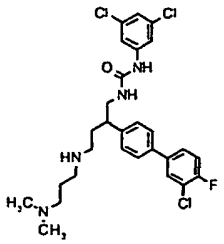
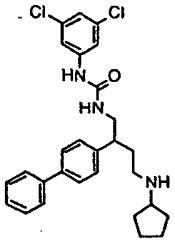
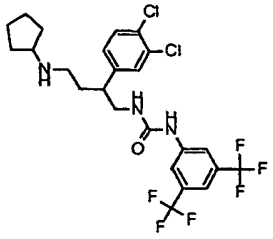




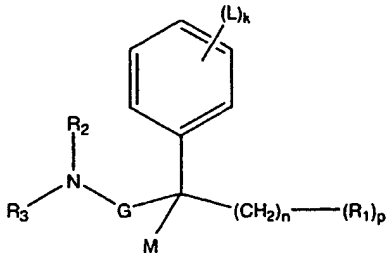






37. A compound, including enantiomers, stereoisomers, rotamers, tautomers and prodrug of said compound, and pharmaceutically acceptable salts or solvates

of said compound or of said prodrug, said compound having the general structure shown in Formula III:



Formula III

wherein:

M is H or R;

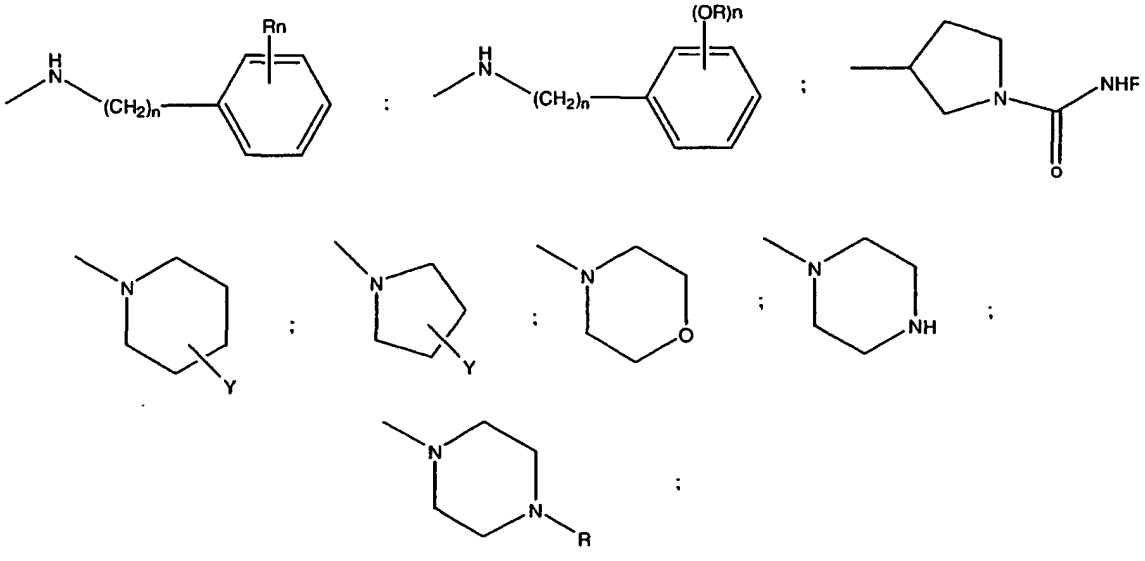
k = 0 to 5;

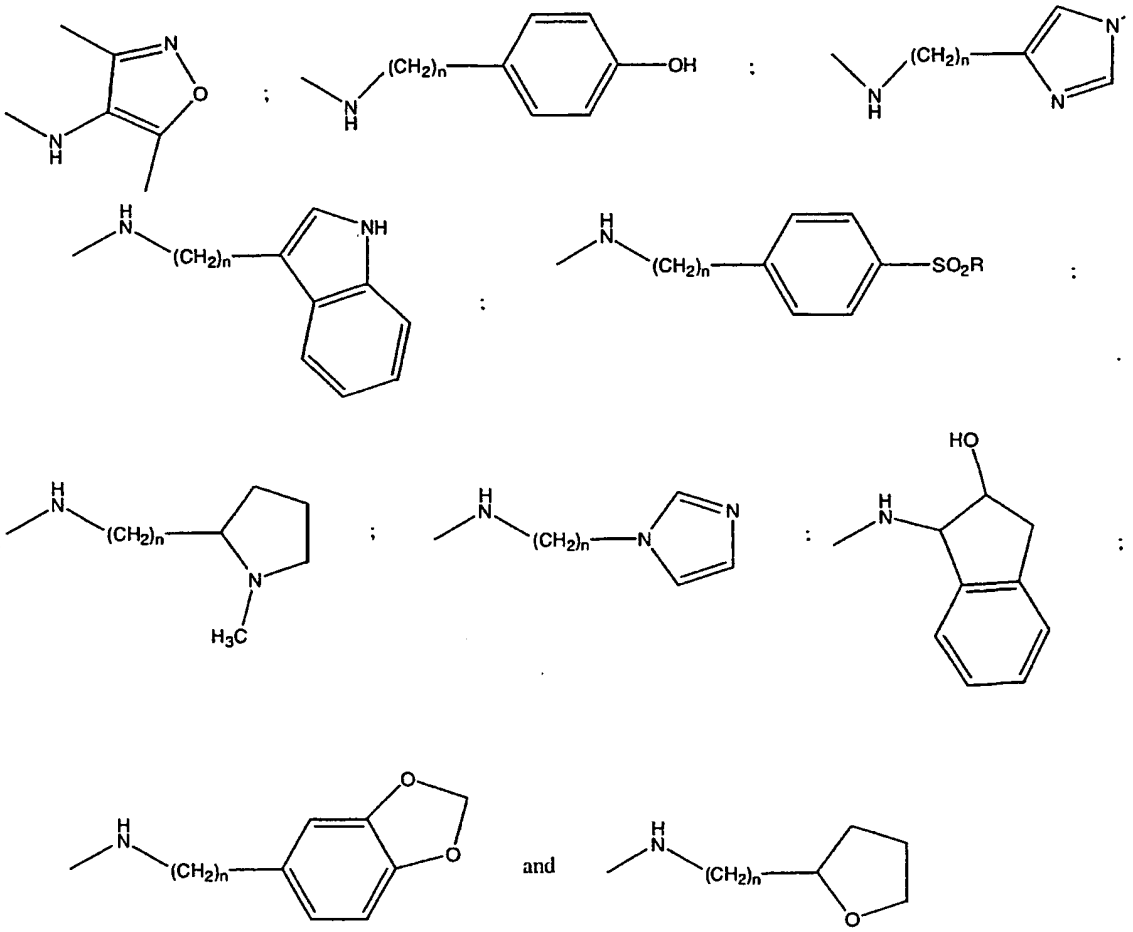
p = 1 to 6;

n = 0 to 6;

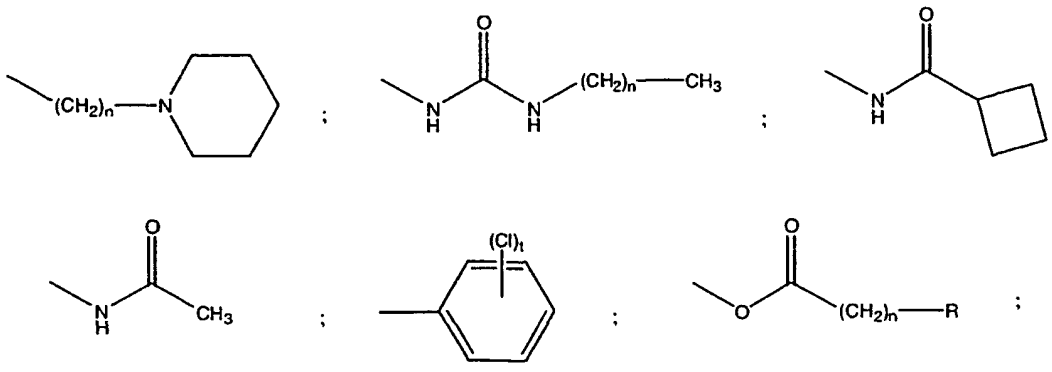
G is a moiety selected from the group consisting of $-CH_2-$, -C(O)- and –C(O)-O- with the –C(O) linked to the $N(R_1R_2)$ in the figure;

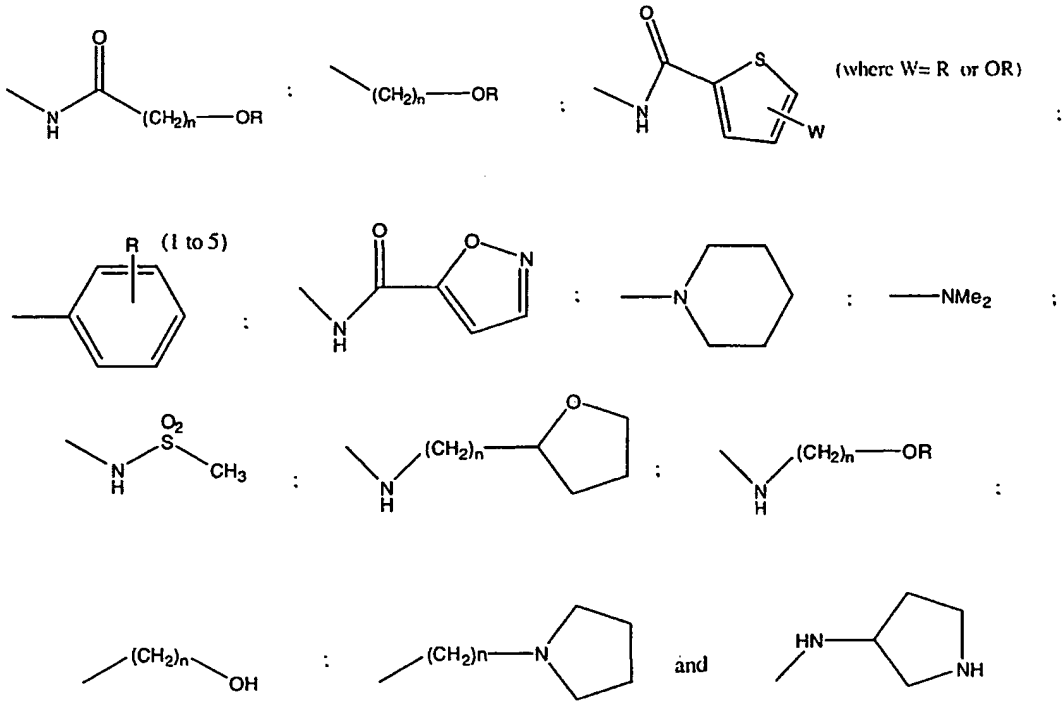
R_1 may be the same or different and are independently selected from the group consisting of R; NH_2; NHR; $N(R)_2$; $N(R)_2 \longrightarrow O$; $NH(CH_2)_nOR$; $N(R)SO_2R$; $NH(CH_2)_n$-$N(R)_2$; $N(R)SO_2(R)$;





where n and R are defined above and Y is a moiety numbering 0 to 5 which may be the same or different and are independently selected from the group consisting of H; OH; NH_2;





where n is defined above and t = 1 to 5;

R_2 is H or alkyl;

R_3 is selected from the group consisting of alkyl, aryl, arylalkyl and alkylaryl; and

L may be the same or different and is independently selected from the group consisting of H, aryl, alkyl, halogen, alkoxy, aryloxy, arylalkoxy, alkylaryloxy, hydroxy, carboxy, carboalkoxy, cyano, CF_3 and NO_2.

38. A pharmaceutical composition for treating disorders associated with the MCH receptor, said composition comprising therapeutically effective amounts of at least one compound of claim 36 and a pharmaceutically acceptable carrier.

39. A pharmaceutical composition to treat eating disorders said composition comprising:

therapeutically effective amounts of at least one compound of claim 1 or of claim 20, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug;

therapeutically effective amounts of one or more compounds, said compounds being selected from the group consisting of a β_3 agonist, a thryomimetic agent, an antiobesity agent, an anorectic agent and an NPY antagonist; and

a pharmaceutically acceptable carrier.

40. A method of treating eating disorders which method comprises administering to a mammal in need of such treatment:

(a) therapeutically effective amounts of at least one compound of claim 1 or of claim 20, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug; and

(b) therapeutically effective amounts of one or more compounds, said compounds being selected from the group consisting of a β_3 agonist, a thryomimetic agent, an antiobesity agent, an anorectic agent and an NPY antagonist; wherein the amounts in (a) and (b) result in said treatment.

41. A pharmaceutical composition to treat eating disorders said composition comprising:

therapeutically effective amounts of at least one compound of claim 1 or of claim 20, a prodrug thereof, or a pharmaceutically acceptable salt of said compound or of said prodrug;

therapeutically effective amounts of one or more compounds selected from the group consisting of an analdose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase 1B inhibitor, a dipeptidyl protease inhibitor, insulin, an insulin mimetic, metformin, acarbose, a PPAR-gamma ligand, rosaglitazone, pioglitazone, GW-1929, a sulfonylurea, glipazide, glyburide, and chlorpropamide; and

a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 02/08300

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C275/40 A61P3/04 A61P3/10 A61K31/17 A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BEILSTEIN Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IGARASHI, HARUYOSHI ET AL: "Synthesis and pharmacology of basic, sec-, and tert-alcohol, and derivatives" retrieved from STN Database accession no. 79:52912 XP002208285 RN abstract & YAKUGAKU ZASSHI (1973), 93(5), 554-65 , — -/--	37

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2002	16/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bedel, C

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 02/08300

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SCHULTZ, KATJA ET AL: "Total synthesis of (+)-(8S,13R)-cyclocelabenzine" retrieved from STN Database accession no. 125:222242 XP002208286 abstract & HELVETICA CHIMICA ACTA (1996), 79(5), 1295-1304 ,	20-23
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 4319271 XP002208287 abstract & CHERKASHIN M.I.: DOKL.CHEM.(ENGL.TRANSL.), 'Online! vol. 313, no. 1.3, 1990, pages 206-209,	20-23,26
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2787871 XP002208288 abstract & JULIA,M.: BULL.SOC.CHIM.FR., 1966, pages 1335-1342,	20,21, 23,26,27
X	ORNSTEIN,PAUL,L.: "Biarylpropylsulfonamides as Novel, Potent Potentiators of AMPA Receptors" J.MED.CHEM., no. 43, 2000, pages 4354-4358, XP002208284 page 4356; example 5G; table 1	1-3,5, 11,12
X	EP 0 432 442 A (WARNER LAMBERT CO) 19 June 1991 (1991-06-19) page 10, line 5 - line 9; example 1B	20-24

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 02/08300

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	O'BRIEN P M ET AL: "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 8. Incorporation of amide or amine functionalities into a series of disubstituted ureas and carbamates. Effects on ACAT inhibition in vitro and efficacy in vivo" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 12, 1994, pages 1810-1822, XP002082610 ISSN: 0022-2623 page 1816; example 9KPRIME; table 5	20,22-24
A	EP 0 955 293 A (BANYU PHARMA CO LTD) 10 November 1999 (1999-11-10) cited in the application claims 1,11,12	1,20
A	EP 0 068 669 A (BEECHAM GROUP PLC) 5 January 1983 (1983-01-05) page 56; table 5	1,20
A	LEB M ET AL: "MELANIN CONCENTRATING HORMONE ANALOGUES: CONTRACTION OF THE CYCLIC STRUCTURE. II. ANTAGONISTS ACTIVITY" LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, vol. 44, no. 7, 1989, pages 451-457, XP002070892 ISSN: 0024-3205 the whole document	1,20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/08300

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 31-33, 40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [X] Claims Nos.: 20-35, 37,39-41 (all of them partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 20-35, 37,39-41 (all of them partly)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to:.....

The compounds given in Formula I as defined in claim 1, the compounds of formula II where n =1-6, R1 is not R and Z is Ar2-C(O), Ar2-NH-C(O) and Ar2-SO2 and the compounds of formula (III) where n=1-6, R1 is not R, G is not CH2 and L is an halogen as well as their use as MCH antagonists. The documents cited from Beilstein in the search report are a mere sample of the many documents retrieved that destroy the novelty of claims 20 and 37.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Inte onal Application No
PCT/US 02/08300

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